Pulmonary Function Measurement in Noninvasive Ventilatory Support

Antonio M. Esquinas
Editor

MOREMEDIA

Springer

Pulmonary Function Measurement in Noninvasive Ventilatory Support

Antonio M. Esquinas
Editor

Pulmonary Function Measurement in Noninvasive Ventilatory Support

Springer

Editor
Antonio M. Esquinas
Intensive Care Unit
Hospital General Universitario Morales Meseguer
Murcia
Spain

ISBN 978-3-030-76196-7 ISBN 978-3-030-76197-4 (eBook)
https://doi.org/10.1007/978-3-030-76197-4

© The Editor(s) (if applicable) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2021
This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The development of noninvasive mechanical ventilation in recent decades has led to the need for exhaustive precision in its indications, application, methodology, as well as aspects such as monitoring and knowing the prognosis. However, the most interesting and fascinating facets such as the behavior, evaluation, and interrelation of lung function with the known physiological effects of noninvasive mechanical ventilation remain unknown. Few books have been dedicated to this respect, thus we believe that this book opens and offers to the clinician a new and original insight on how this interrelation between pulmonary function tests and the known effects of noninvasive mechanical ventilation in the short and long term can be understood for making decisions. For this aim, we have developed the table of contents, as well as classified and analyzed the pulmonary function tests in various pathologies most frequently used with a special focus on how they can be used in practical protocols. Moreover, the reader can find what results can be analyzed and known to be able to develop treatment strategies most frequently adapted to lung function and, most importantly, also be able to predict the patient's prognosis.

In **Pulmonary Function Measurement in Noninvasive Ventilatory Support,** chapters are presented as an essential source of information for the clinician and tools in daily practice.

Being able to predict based on a correct evaluation of lung function in noninvasive mechanical ventilation is a solid basis for an essential application and evaluation.

The future depends on what we do in the present—(Mahatma Gandhi)

Murcia, Spain
March 2021

Antonio M. Esquinas

Contents

Part II Noninvasive Ventilation: Pulmonary Function Measurements—Classification, Screening Test and Questionnaires

Abbreviations

6MWT	6-minute walk test
A	Alveolar
A	Surface area of the tissue
AAA	Abdominal aortic aneurysms
AAEs	Acute asthma exacerbations
AASM	American Academy of Sleep Medicine
ABG	Arterial blood gas
ACCF	American College of Cardiology Foundation
ACOS	Asthma and COPD overlap syndrome
ACPE	Acute Cardiogenic Pulmonary Oedema
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADA	American Diabetes Association
AECOPD	Acute exacerbations of chronic obstructive pulmonary disease
AHA	American Heart Association
AHI	Apnea hypopnea index
AHRF	Acute hypoxemic respiratory failure
AHRQ	Agency for Healthcare Research and Quality
ALI	Acute lung injury
ALS	Amyotrophic lateral sclerosis
APACHE II	Acute Physiology and Chronic Health Evaluation II
APAP	Automatic positive airway pressure
APRV	Airway pressure release ventilation
AQLQ	Asthma Quality of Life Questionnaire
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ARTP	Association for Respiratory Technology and Physiology
ASV	Adaptive servo ventilation
ATS	American Thoracic Society
ATS/ERS	American Thoracic Society/European Respiratory Society
AutoPEEP	Unintended positive end-expiratory pressure
AVAPS	Average volume-assured pressure support ventilation
BDI	Baseline dyspnea index
BDI	Beck depression inventory
BDP	Bilateral diaphragmatic paralysis

BE	Base excess
BEV	Back extrapolated volume
BG	Blood gases
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Barometric pressure
BPAP	Bilevel positive airway pressure
BTS	British Thoracic Society
BTS/RCP	British Thoracic Society/Royal College of Physicians
C	Concentration
C3–C5	Cervical segments three, four, and five
$Ca{=}vO_2$	Arterio-Venous difference Oxygen Concentration
CAM	Confusion Assessment Method
CaO_2	Systemic Arterial Oxygen Concentration
CAT	COPD Assessment Test
CC 16	Club cell protein 16
CCQ	COPD Control Questionnaire
CCW	Chest wall compliance
CDT	Clock Drawing Test
Cdyn	Dynamic compliance
CF	Cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFTR	Cystic fibrosis transmembrane conductance regulator
CGA	Comprehensive Geriatric Assessment
CH_2O	Water vapor concentration
CHF	Chronic heart failure
CL	Lung compliance
cmH_2O	Centimeters of water
CN_2	Nitrogen concentration
CNEP	Continuous negative extrathoracic pressure
CNS	Central nervous system
CO	Carbon monoxide
CO	Cardiac output
CO_2	Carbon dioxide
CO_2	Oxygen concentration
CompSA	Complex sleep apnea
COPD	Chronic obstructive lung disease
COT	Conventional oxygen therapy
COVID-19	Coronavirus disease-19
CPAP	Continuous positive airways pressure
CPE	Cardiogenic pulmonary edema
CPET	Cardiopulmonary exercise testing
CPP	Cerebral perfusion pressure
$CpvO_2$	Pulmonary venous oxygen concentration
CR 10	10 Category-ratio
CRD	Chronic respiratory diseases
CRF	Chronic respiratory failure

CRQ	Chronic Respiratory Questionnaire
CRQ-SAS	Chronic Respiratory Questionnaire Self-Administered Standardized Format
CRS	Respiratory system compliance
CSA	Central sleep apnea
CSB	Cheyne-Stokes breathing
CSCI	Cervical spinal cord injury
Cstat	Static compliance
CT	Computed tomography
CV	Closing volume
CVO_2	Pulmonary arterial oxygen concentration
CWD	Chest wall disease
D	Diffusion coefficient
DD	Diaphragmatic dysfunction
DLCO	Diffusing capacity for carbon monoxide
DLO_2	Lung diffusing capacity
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
DNI	Do not intubate
DO_2	Oxygen delivery
DTF	Diaphragm thickening fraction
DU	Diaphragm ultrasonography
Eadi	Electrical activity of the diaphragm
EBC	Exhaled breath condensate
ECCS	European Community of Coal and Steel
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EFL	Expiratory flow limitation during tidal breathing
EGA	Emogasanalysis
EGFR	Epidermal growth factor receptor
ELBG	Ear lobe blood gas
EMG	Electromyography
EMT	Expiratory muscle training
EOFE	End of forced expiration
EOT	End of Test
EPAP	Expiratory positive airway pressure
EQ	VAS The EuroQol Visual Analog Scale
ER	Emergency room
ERS	European Respiratory
ERV	End expiratory volume
ESC	European Society of Cardiology
$etCO_2$	End-tidal carbon dioxide
ETI	Endotracheal intubation
EXIT	Executive interview
FAB	Frontal assessment battery
FACQ	Alveolar carbon monoxide fraction
FAO_2	Oxygen concentration in alveolar air

$FECO_2$	Carbon dioxide concentration in expired air
FEF25-75	Forced expiratory flow between 25 and 75% of the forced vital capacity
FENO	Fractional excretion of nitric oxide
FEO_2	Oxygen concentration in expired air
FET	Forced expiratory time
FEV	Forced expiratory volume
FEV1	Forced expiratory volume in one second
$FiCO_2$	Carbon dioxide concentration in inspired air
FiO_2	Fraction of inspired oxygen
FIVC	Forced inspiratory vital capacity
FOT	Forced oscillation technique
FPD	Fine particle dose
FPF	Fine particle fraction
FRC	Functional residual capacity
Fres	Resonant frequency
FSS	Fatigue Severity Scale
FVC	Forced vital capacity
GCS	Glasgow Coma Scale
GDS	Geriatric Depression Scale
GINA	Global Initiative for Asthma
GLI	The Global Lung Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPB	Glossopharyngeal breathing
h	Hour
HADS	Hospital Anxiety and Depression Scale
Hb	Hemoglobin
HbO_2	Oxyhemoglobin
HCO_3	Hydrogen carbonate concentration
HDU	High Dependency Unit
He	Helium
HF	Heart failure
HFNC	High flow nasal cannula
HFOV	High frequency oscillatory ventilation
HFPV	High frequency percussive ventilation
HMV	Home mechanical ventilation
HNP	Human neutrophil peptide
HRCT	High resolution computed tomography
HRF	Hypercapnic respiratory failure
HRQL	Health-related quality of life
HZ	Hertz
I/R	Inspiration/expiration ratio
IADL	Instrumental activities of daily living
IAPV	Intermittent abdominal compression ventilation
IC	Inspiratory capacity
IC	Inspiratory capacity
ICAM-1	Intracellular adhesion molecule-1
ICAM-2	Intracellular adhesion molecule-2

ICEP	Idiopathic chronic eosinophilic pneumonia
ICP	Intracranial pressure
ICS	Intensive Care Society
ICU	Intensive Care Unit
IGFBP-2	Insulin-like growth factor binding protein 2
IL-8	Interleukin 8
ILD	Interstitial lung diseases
IMT	Inspiratory muscle training
IMV	Invasive mechanical ventilation
INQoL	Individualized Neuromuscular Quality of Life Questionnaire
IOS	Impulse oscillometry system
IPAP	Inspiratory positive airway pressure
iPEEP	Intrinsic positive end-expiratory pressure
IPF	Idiopathic pulmonary fibrosis
IPPV	Intermittent positive pressure ventilation
IRV	Inspiratory reserve volume
ISO	International Organization for Standardization
ISWT	Incremental shuttle walk test
iVAPS	Intelligent volume-assured pressure support
IVC	Inspiratory vital capacity
JN	Jet nebulizer
KL-6	Krebs von den Lungen-6
KS	Kyphoscoliosis
L	Liter
LA	Left atrium
LAM	Lymphangioleiomyomatosis
LCADL	London Chest Activity of Daily Living Scale
LCI	Lung clearance index
LLN	Lower limits of normal
LTOT	Long-term oxygen therapy
LU	Lung ultrasonography
MAP	Mean airway pressure
MCI	Mild cognitive impairment
MEP	Maximum expiratory pressure
MFS	Marfan syndrome
MIE	Mechanical insufflation exsufflation
min	Minute
MIP	Maximal inspiratory pressure
mm^2	Square meters
MMAD	Mass median aerodynamic diameter
MMEF	Maximum mid expiratory flow
mmHg	Millimeter of mercury
MMP	Matrix metalloproteinase
mMRC	Modified Medical Research Council
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
mPAP	Mean pulmonary arterial pressure

MPV	Mouthpiece ventilation
MRC	Medical Research Council
MRF 26	Maugeri Respiratory Failure Questionnaire
MRI	Magnetic resonance imaging
MV	Mechanical ventilation
MVV	Maximal voluntary ventilation
MW	Molecular weight
NAVA	Neurally adjusted ventilatory assist
NCF	Non-cystic fibrosis
NE	Neutrophil elastase
NEEP	Negative end-expiratory pressure
NIMV	Noninvasive mechanical ventilation
NIPPV	Noninvasive positive pressure ventilation
NIV	Noninvasive ventilation
NMD	Neuromuscular disease
NMES	Neuromuscular electrical stimulation
NPPV	Noninvasive positive pressure ventilation
NPV	Negative pressure ventilation
NREM	Non-rapid eye movement
N_2	Nitrogen
O_2	Oxygen
O_2COB	Oxygen cost of breathing
O_2ER	Oxygen extraction ratio
OBS	Obesity hypoventilation syndrome
OCD	Oxygen cost diagram
OHS	Obesity hypoventilation syndrome
OI	Oxygenation index
OSA	Obstructive sleep apnea
P	Partial pressure
P0.1	Airway occlusion pressure
PA–aO_2	Alveolar-arterial oxygen partial pressure difference
PaCO	Partial pressure of carbon monoxide
$PACO_2$	Alveolar carbon dioxide partial pressure
PA–CO_2	Alveolar-capillary oxygen partial pressure difference
$PaCO_2$	Arterial carbon dioxide partial pressure
$PaCO_2$	Arterial carbon dioxide tension
PAH	Pulmonary arterial hypertension
PaO_2	Arterial partial pressure of oxygen
PaO_2/FiO_2	Arterial partial pressure of oxygen/fraction of inspired oxygen
PAP	Positive airway pressure
Patm	Atmospheric pressure
PAV	Proportional assist ventilation
PAWP	Pulmonary arterial wedge pressure
PCF	Peak cough flow
PCO_2	Partial pressure CO_2
PCV	Pressure-controlled ventilation
Pdi	Transdiaphragmatic pressure

PE	Pulmonary embolism
$PECO_2$	Mixed expired carbon dioxide
PEEP	Positive end-expiratory pressure
PEEPi	Intrinsic positive end-expiratory pressure
PEF	Peak expiratory flow
PEF	Peak expiratory flow
PE_{max}	Maximum static expiratory pressure
PEO_2	Mixed expired oxygen
Pes	Esophageal pressure
PES	Pediatric Endocrine Society
PET	Positron emission tomography
$PetCO_2$	End tidal pressure CO_2
PFO	Patent foramen ovale
PFSDQ	Pulmonary Functional Status and Dyspnea Questionnaire
PFT	Pulmonary Function Tests
PH	Pulmonary hypertension
PIF	Peak inspiratory flow
Pi_{max}	Maximal inspiratory pressure
PIP	Positive inspiratory pressure
PNS	Phrenic nerve stimulation
PNSmg	Magnetic phrenic nerve stimulation
PNStc	Transcutaneous electrical phrenic nerve stimulation
PO_2	Oxygen partial pressure
PP	Prone positioning
PPC	Postoperative pulmonary complications
P_{peak}	Peak airway pressure
P_{pl}	Pleural pressure
P_{plat}	Pressure of plateau
$P_{plateau}$	Plateau pressure
PR	Pulmonary rehabilitation
ProBNP	Pro-brain natriuretic peptide
PS	Pressure support
PSG	Polysomnography
PSV	Pressure support ventilation
$PtcCO_2$	Transcutaneous pressure of CO_2
$PtCO_2$	Tissue carbon dioxide partial pressure
PtO_2	Tissue oxygen partial pressure
P_{total}	Total pressure
PTP	Pressure time product
PTPdi	Diaphragmatic pressure time product
PVD	Patient-ventilator dyssynchrony
PVR	Pulmonary vascular resistance
Pinspired O_2 PiO_2	Oxygen partial pressure in inspired air
Q	Lung Perfusion Pulmonary Blood Flow
QoL	Quality of life
QOL-B	Quality of Life Questionnaire for Bronchiectasis
R5-R20	Difference between the high 20 Hz and low 5 Hz frequency signals

RA	Right atrium
RCT	Randomized control trial
RCTs	Randomized controlled trials
REM	Rapid eye movement
RF	Respiratory failure
RGAs	Rapid gas analyzers
RHDU	Respiratory High Dependency Unit
RICU	Respiratory Intensive Care Unit
RMS	Respiratory muscle strength
ROS	Reactive oxygen species
RPE	Rate of perceived exertion
RQ	Respiratory quotient
RR	Respiratory rate
RV	Right ventricular
SABAs	Short-acting beta-agonists
SAMAs	Short-acting muscarinic antagonists
SaO	Oxygen saturation
SaO_2	Arterial blood oxygen saturation
SAPS	Simplified Acute Physiology Score
SCI	Spinal cord injury
SDB	Sleep-disordered breathing
SF-12	The 12 Item Short Form Health Survey
SF-36	The 36 Item Short Form Survey
SGRQ	St. George's Respiratory Questionnaire
SIII	Slope of Phase III
SMA	Spinal muscle atrophy
SMWT	Six-minute walk test
SNIP	Sniff nasal inspiratory pressure
SOD	Superoxide dismutase
SOFA	Sequential Organ Failure Assessment
Sol	Gas solubility
SPA	Surfactant protein A
SPD	Surfactant protein D
SPECT	Single photon emission computed tomography
SpO_2	Oxygen saturation
SPS	Serratus posterior superior
sRAGE	Soluble receptor for advanced glycation endproducts
sRaw	Specific airway resistance
SRI	Severe respiratory insufficiency
SRIQ	Severe Respiratory Insufficiency Questionnaire
ST	Spontaneous time
SVC	Slow vital capacity
SvO_2	Mixed venous oxygen saturation
$TcCO_2$	Transcutaneous carbon dioxide
$tcPCO_2$	Transcutaneous PCO_2
TDI	Transition dyspnea index
Te	Expiratory time
TF	Thickening fraction

Ti	Inspiratory time
TLC	Total lung capacity
TLC	Total lung capacity
TNFα	Tumor necrosis factor-α
TOS	Total oxidative status
TV	Tidal volume
twitch Pdi	Bilateral transcutaneous phrenic nerve stimulation
twPdi	Twitch transdiaphragmatic pressure
USA	United States of America
μm	Micrometer
V'CO_2	CO_2 production
V'E	Minute ventilation
V'E	Ventilation/minute
V'gas	Rate of a gas diffusion
VA	Alveolar ventilation
Va	Alveolar volume
VAS	Visual Analog Scale
VATS	Video-assisted thoracoscopic surgery
VC	Vital capacity
VCO_2	Ratio of carbon dioxide production
VCV	Volume controlled ventilation
VD	Ventilation of the dead space
VE	Exhaled volume/breath
VEGF	Vascular endothelial growth factor
VI	Per minute inspired air volume
VILI	Ventilator-induced lung injury
VMN	Vibrating mesh nebulizer
VO_2 max	Maximal oxygen consumption
VO_2	Ratio of Oxygen consumption
VOCs	Volatile organic compounds
V_T	Tidal volume
VTE	Expiratory vital volume
V_{TI}	Inspired tidal volume
V_{total}	Total ventilation
V_{tPS}	Volume targeted pressure support
WHO	World Health Organization
WOB	Work of breathing
WU	Wood units

List of Videos

Video 36.1

Electronic Supplementary Material is available in the online version of the related chapter on SpringerLink: https://doi.org/10.1007/978-3-030-76197-4

Part I

Noninvasive Ventilation: Basic Physiology and Pulmonary Function Measurements

Spontaneous Breathing. Physiology

1

M. I. Matias, G. Gonçalves, C. Cortesão, P. S. Santos, and Antonio M. Esquinas

Abstract

The respiratory system consists of a set of organs whose structure is able to perform numerous functions of which the cardinal function is breathing. To perform its cardinal function, three basic steps, ventilation, perfusion, and diffusion need to occur in perfect conjunction. This is achieved through feedforward and feedback signaling which allow the capture and transport of oxygen (O_2) and carbon dioxide (CO_2) adjusted to metabolic needs at all times.

Keywords

Spontaneous breathing · Ventilation · Lung perfusion · Gas diffusion · Breathing regulation

Abbreviations

CO_2	Carbon dioxide
Hb	Hemoglobin
O_2	Oxygen
$PaCo_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PO_2	Oxygen partial pressure

1.1 Introduction

The respiratory system consists of a set of organs whose structure is able to perform numerous functions of which the cardinal function is breathing.

Breathing consists of the uptake of oxygen from the atmosphere and its transfer to the blood and the metabolism of the cells in conjunction with the elimination of carbon dioxide from that metabolism to the outside.

To allow contact between the air in the environment and the blood, an anatomical path is needed and three basic steps, ventilation, perfusion, and diffusion should be performed in perfect conjunction.

Breathing must be adapted to the body's metabolic requirements at all times, only possible due to a complex system of regulation involving the

M. I. Matias (✉) · G. Gonçalves · C. Cortesão
P. S. Santos
Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_1

respiratory centers, that integrate the information received from various receptors and elaborates suitable response through the effector muscles and this loop continues [1].

1.2 Discussion and Analysis of the Main Topic

1.2.1 Anatomy and Function

To enable contact with the bloodstream, the air goes through the upper airways (nose/mouth, pharynx, and larynx) and reaches the lower airways starting in the trachea. The trachea then divides into right and left main bronchi, and these divide subsequently, becoming narrower and shorter, ending in the alveolar ducts, laden with alveoli where gas exchange occurs [1].

The lower respiratory system exists within a muscle, bone, and ligament structure that surrounds it, and is called the thoracic cavity. The diaphragm is its base and above there is the costal wall, formed by the succession of the costal arches joined by the intercostal muscles.

The lung parenchyma is involved by a two-layer membrane, the visceral pleura covering the lung and interlobar fissures and the parietal pleura covering the chest wall, diaphragm, and mediastinum [1, 2].

These structures together perform several functions like the function of phonation or the role in pH balance of the body through the fast bicarbonate-CO_2 system. Additionally, being in great contact with the outside environment, the lung also plays an important part in removing of inhaled foreign particles, also it is able to secrete immunoglobulins like IgA in the bronchial mucus that contribute to its defenses against infection. The endocrine organ should be highlighted, when several vasoactive and bronchoactive substances are metabolized in the lung and may be released into the circulation under certain conditions, for example, the conversion of angiotensin I, catalyzed by the angiotensin-converting enzyme, located in small pits in the surface of the capillary endothelial cells [3].

However, to perform its cardinal function, three basic steps need to occur: **ventilation, perfusion,** and **diffusion.**

1.2.2 Ventilation

Ventilation is the passage of air into and out of the airways, with the goal of reaching the alveoli. Pulmonary ventilation depends on three types of pressure: atmospheric pressure, alveolar pressure, and pleural pressure. Atmospheric pressure is the force exerted in any surface by gases in the air surrounding it. Alveolar pressure changes with breathing and corresponds to the pressure of the air within the alveoli while pleural pressure is the negative pressure (inferior to atmospheric pressure) originated by the elasticity of the chest wall, which tends to distend, opposite to the lung parenchyma, which tends to contract [1].

In inspiration, there is an elevation of the ribs and forward movement of the sternum due to intercostal muscles action and flattening of the diaphragm, increasing the capacity of the thorax. This causes the pleural pressure to become more negative and due to the adhesive nature of the pleural fluid, this forces the lung to follow the thoracic expansion. As a consequence, the alveoli distend and the pressure inside them drops below atmospheric pressure, creating a pressure gradient (between the atmosphere and the alveoli), that makes the atmospheric air penetrate through the bronchial tree. Expiration on the other hand, under normal conditions, it is a passive phenomenon which occurs by relaxation of the structures contracted in inspiration. When the inspiratory muscles relax, the chest wall retracts, compressing the lungs inside it, originating in the alveoli, a pressure superior to the atmospheric pressure, causing air to go out of the bronchial tree [1, 4, 5].

Mechanics of ventilation all in all depends on the elasticity of the thorax and lung tissue, resistance to air friction in the airways, resistance to tissue sliding between them, and strength of the respiratory muscles.

Moreover, lung ventilation is not uniform, in the normal lung there are regional ventilation dif-

ferences mainly due to gravity. In orthostatic position, the alveoli of lung apex are more expanded and stiffer, while alveoli of the lung base have a smaller diameter, contain a smaller air volume at rest, but expand better on inspiration and therefore are better ventilated.

At rest a human being breathes 12–16 times a minute, mobilizing about 500 ml of air in each cycle. This air volume is designated as a tidal volume. A 500 ml of tidal volume with a breathing frequency of 12–16 cycles per minute results in 6–8 L of volume/minute or ventilation/minute. However, the air must pass through the conducting airways and only a portion will penetrate the alveoli to be available for gas exchange. The air that does not reach the alveoli is called anatomical dead space. Also, a part of the air that reaches the alveoli will not come into contact with the capillary wall, making diffusion impossible, this is called the alveolar dead space. The sum of the two dead spaces is called total dead space or physiological which is totally ineffective for gas exchange. Normally is about 150 ml but if there is inequality of blood flow and ventilation in a diseased lung the physiologic dead space may be much higher [1, 2, 4].

1.2.3 Lung Circulation/Perfusion

The pulmonary circulation receives mixed venous blood from the right ventricle through the main pulmonary artery which divides into smaller arteries following the bronchial tree and that subsequently form a dense network of capillaries that facilitate diffusion. These capillaries then carry oxygenated blood through small pulmonary veins that later form four large veins that end in the left atrium. Additionally, the lung has another blood system that supplies the airways, the bronchial circulation [1].

The pulmonary circulation has different characteristics than the systemic circulation because although all the cardiac output passes through the pulmonary circulation, its vessels are more malleable and can quickly experience large variations in caliber, therefore, the pulmonary arterial pressure is low. Moreover, there is a pressure gradient meaning that the blood distribution is uneven and depends mainly on the hydrostatic pressure and collapsibility of the pulmonary vessels that can easily extend or collapse. During inspiration, lung expansion occurs, and the capillaries surrounded by alveoli are compressed and may collapse if the alveolar pressure is greater than the blood pressure in the capillary. And finally, there is also the effect of gravity in pulmonary circulation that causes the lung regions located below the heart level to be perfused better in the orthostatic position.

Pulmonary perfusion refers to the blood flow of the pulmonary circulation available for gas exchange, it has regional differences in the lungs that are directly influenced by the balance of three forces: alveolar pressure, intra-arterial pressure, and venous pressure. West [1] described three lung regions according to the relationship between blood and alveolar pressures along the lung.

- *Zone I (apical)*: The pressure inside the alveoli is greater than the intra-arterial pressure, causing the capillaries to collapse, reducing the blood flow in this area.
- *Zone II (intermediate)*: The intra-arterial pressure is greater than the alveolar pressure, the latter being greater than the venous pressure. Thus, the capillaries are distended in the arterial segment and more or less collapsed in the venous. The output is controlled by the pressure gradient existing between the arterial segment and the alveolus, resulting in the existence of flow only in the systolic peaks, an intermittent flow. Here, the venous pressure has no effect on the flow because it is lower than the atmospheric pressure in this area of the lung.
- *Zone III (lower third of the lung)*: The venous pressure is greater than the alveolar and intra-arterial pressure. The vessels are permanently distended here and the driving force of the output lies mainly in the pressure gradient between the artery and the vein, thus being continuous flow. In resting conditions, it is the

zone III that functions and only during the effort are gradually used vessels from zones II and I.

Although passive factors dominate blood flow regulation, pulmonary vasoconstriction may occur after the reduction of PO_2 of alveolar gas, reducing blood flow in poorly ventilated regions of the lung [1, 2].

1.2.4 Diffusion

Pulmonary diffusion is an essentially physical phenomenon, through which there is the passage of oxygen from the alveoli to the capillaries and carbon dioxide in the opposite direction. This is performed, through the thin alveolus-capillary barrier, which allows the transfer of these gases, available at different pressures in two physical phases, blood and air [1].

In respect to oxygen diffusion, at the point where the venous blood reaches the capillaries, the pressure gradient through the alveolar-capillary membrane favors the entry of O_2 to the capillary blood and diffusion occurs. In capillaries, oxygen is transported in a tiny portion in physical solution but mostly combined with hemoglobin (Hb). The amount of O_2 carried by Hb presents a non-linear relationship with the partial pressure of oxygen in arterial blood, presents a sigmoid or S curve, called HbO_2 dissociation curve [1].

Regarding carbon dioxide diffusion, the CO_2 from the metabolism passes from the cells to the capillaries, circulating in part dissolved in the plasma and in part in the chemical bond. At the point where the venous blood reaches the capillaries, carbon dioxide pressure gradient through the alveolar-capillary favors the exit of CO_2 into the alveolus. These phenomena are further explained in Chap. 9.

1.2.5 Breathing Regulation

The respiratory muscles require stimulation by the nervous system that produces the pattern of sequential ventilatory inspiration-expiration. This regulation aims to adjust the capture and transport of O_2 and CO_2 to the momentary metabolic needs. It is a complex mechanism, not fully explained, consisting of feedforward and feedback pathways that essentially regulate the rate and depth of breathing.

Ventilation control rests in three core elements: the central control in the brainstem, the effectory muscles that allow breathing movements, and the sensors that generate the input that reflects momentary needs [1, 3].

The ventilatory rhythm is primarily driven by respiratory centers which are groups of neurons dispersed by the reticular substance of the brain stem. There are identified 2 groups of respiratory neurons, the dorsal respiratory group and the ventral respiratory group in the medulla oblongata. For finer regulation of the muscle contraction and also in the genesis of breath-related sensations there are sensory-motor mechanisms. The muscle spindles of the respiratory muscles detect longitude alterations (distension receptors, irritation receptors, J receptors, and mechanoreceptors). The efferent impulses of the receptors are then transmitted to the neuronal centers brain stem which responds accordingly [1].

There is also a chemical regulation of ventilation which keeps partial pressures of O_2 and CO_2 within narrow limits. There are chemosensitive areas in the medulla and peripheral chemoreceptors (highly vascularized structures located in the carotid bifurcation and in the aortic crust) that detect decrease in arterial partial pressure of oxygen (PaO_2), decrease in arterial pH, or increase in arterial partial pressure of carbon dioxide ($PaCO_2$) which trigger increase in ventilation [1–4].

Other sensory systems also can stimulate or inhibit breathing, for example, proprioceptors in limb muscles and joints, but also touch, temperature, and pain, and even excess lung stretch.

Although this regulation is mostly autonomically controlled, in certain circumstances, for example, if unexpected changes are produced, consciousness is acquired and breathing regulation can become voluntary and commanded by cortical areas of the brain [1–4].

Regarding breathing regulation during sleep, there are prominent differences. There is a gen-

eral decrease in respiratory stimulus, lower sensitivity of servomechanisms, namely a higher threshold for CO_2 stimulus, thus occurring periodical variations of the ventilation and $PaCO_2$ [5]. Also, there are major alterations during exercise, the increase of metabolic needs determines a great increase in depth and rate of breathing. These are two major examples of how the respiratory system phenomenally adapts to the body's metabolic requirements at all times, depending on the receptors' inputs in a cyclical manner [6].

1.3 Conclusion Discussion

To conclude, breathing is a very complex body function that adjusts the capture and transport of O_2 and CO_2 to the momentary metabolic needs through a feedforward and feedback signaling.

Key Major Recommendations

- The respiratory system plays multiple functions but breathing is its cardinal function.
- To enable contact between the air in the environment and the blood, three basic steps, ventilation, perfusion, and diffusion should be performed in perfect conjunction.
- Normal lung ventilation is not uniform: alveoli of the lung bases are better ventilated.
- Pulmonary circulation is very different from systemic circulation and blood flow is unevenly distributed.
- Breathing regulation aims to adjust the capture and transport of O_2 and CO_2 to the momentary metabolic needs.

References

1. West JB. Respiratory physiology: the essentials. 9th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012.
2. Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, Siegel MD. Fishman's pulmonary diseases and disorders. 5th ed. New York: McGraw-Hill Medical; 2015.
3. Broaddus C, Mason RJ, Ernst JD, King TE, Lazarus SC, Murray JF, Nadel JA, Slutsky AS, Gotway MB. Murray and Nadel's textbook of respiratory medicine. 6th ed. London: W.B. Saunders; 2016. p. 44–75.
4. Mortola JP. How to breathe? Respiratory mechanics and breathing pattern. Respir Physiol Neurobiol. 2019;261:48–54. https://doi.org/10.1016/j.resp.2018.12.005.
5. Ratnovsky A, Gino O, Naftali S. The impact of breathing pattern and rate on inspiratory muscles activity. Technol Health Care. 2017;25(5):823–30. https://doi.org/10.3233/THC-170826.
6. Kryger M. Sleep and breathing disorders. 1st ed. Philadelphia, PA: Elsevier; 2017. p. 63–9.

2 Dyspnea, Pathophysiology in Acute and Chronic Respiratory Failure

Bruno Cabrita, Gil Gonçalves, André Cabrita, and Antonio M. Esquinas

Abstract

Dyspnea is a complex subjective symptom, variable between patients. It may present with acute or chronic onset. There are multiple causes of dyspnea, including a normal reaction to intense efforts, or association with disorders, usually pulmonary or heart diseases, with significant limitations on daily-life activities and quality of life. Many causes of dyspnea are the causes of respiratory failure.

Keywords

Dyspnea · Respiratory · Failure

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BDI	Baseline dyspnea index
BNP	Brain natriuretic peptide
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CR 10	10 category-ratio
CRF	Chronic respiratory failure
IPF	Idiopathic pulmonary fibrosis
IV	Invasive ventilation
LCADL	London chest activity of daily living scale
mMRC	Modified medical research council
NIV	Noninvasive ventilation
OCD	Oxygen cost diagram
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PaO_2/FiO_2	Arterial partial pressure of oxygen/fraction of inspired oxygen
PEEPi	Intrinsic positive end-expiratory pressure
PFSDQ	Pulmonary functional status and dyspnea questionnaire
PR	Pulmonary rehabilitation
RF	Respiratory failure

B. Cabrita (✉)
Pulmonology Department, Hospital Pedro Hispano, Matosinhos, Portugal

G. Gonçalves
Pulmonology Department, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

A. Cabrita
Cardiology Department, Centro Hospitalar Universitário São João, Porto, Portugal

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_2

RPE	Rating of perceived exertion
TDI	Transition dyspnea index
V'CO_2	CO_2 production
V'E	Ventilation/minute
VAS	Visual analogue scale

2.1 Introduction

2.1.1 Definition

Dyspnea is a complex symptom, a subjective feeling of breathlessness, breathing discomfort, chest tightness, and air hunger. It is variable between patients and may have an acute or chronic onset [1]. It is highly influenced by many factors, including patients' past experiences, physiology and psychological characteristics, social interactions, beliefs, and also environmental factors [1].

Dyspnea may be a normal symptom associated with heavy efforts, but may also be associated with disorders, mainly pulmonary and/or heart diseases, and occur more often, even with small activities or at rest, with significant limitation in daily-life activities and impact in the quality of life [1].

Many causes of dyspnea also cause the development of respiratory failure (RF).

2.2 Discussion and Analysis of the Main Topic

2.2.1 Pathophysiology of Dyspnea

Dyspnea pathophysiology is complex and may be multifactorial. It usually occurs due to a compromise in the cardiovascular or respiratory systems, or, in other cases, due to metabolic impairment, neuromuscular disorders, or have a psychological component [1].

The respiratory effort occurs when there is a mismatch between pulmonary ventilation and respiratory drive, between afferent receptors in the airways and central respiratory motor activity [1]. There are three main signals responsible for the development of dyspnea [1]:

1. Afferent signals.
2. Central information processing.
3. Efferent signals.

Afferent signals: The respiratory system has specific acid-sensing ion channels, mechanoreceptors, and lung receptors that constitute physiological pathways for the development of dyspnea. Also, they have juxtacapillary receptors, sensitive to pulmonary interstitial edema and stretch receptors sensitive to bronchoconstriction. The carotid bodies and medulla are endowed with chemoreceptors that process the information regarding the state of blood gas levels (O_2, CO_2, and H^+). The muscle spindles in the chest wall detect the stretch and tension of the respiratory muscles and send afferent signals to the central nervous system [1].

Central information processing: The brain processes all the afferent information and develops the efferent responses, according to the required demands of airway pressure, air flow, and lung movement. When a mismatch occurs in this process, or the response of the airways is inappropriate, dyspnea occurs. The respiratory effort is perceived by the sensory cortex activation, resulting in the subjective symptoms of breathlessness. Psychological factors may influence this perception [1].

Efferent signals: Motor output information (efferent motor neuronal signal) is sent by the central nervous system (CNS) to respiratory muscles, especially the diaphragm to adjust the respiratory response [1, 2].

2.2.2 Causes of Dyspnea

The major causes of dyspnea (90%) are related with lung or cardiac disorders, including asthma or chronic obstructive pulmonary disease (COPD), pneumonia, heart failure, arrhythmias, or ischemic heart disease. The different causes of dyspnea are evidenced in Table 2.1 [1].

Table 2.1 Possible causes for the development of dyspnea [1]

Causes of dyspnea
Lung disorders:
Asthma
COPD
Bronchiectasis
Pneumonia
Sarcoidosis
Tuberculosis
Interstitial lung diseases
Thromboembolic pulmonary disease
Pulmonary hypertension
Lung cancer
Obstructive sleep apnea
Pleural effusion
Pneumothorax
Cardiac disorders:
Arrhythmias
Congestive heart failure
Ischemic heart disease
Cardiomyopathy
Myocarditis
Valvular heart disease
Pericarditis
Pericardial effusion
Congenital heart disease
Hematological disorders:
Anemia
Carbon monoxide poisoning
Thrombotic thrombocytopenic purpura
Methaemoglobinemia
Sulfhaemoglobinamia
Abdominal:
Ascites
Gastro-esophageal reflux disease
Metabolic:
Thyroid disease
Cushing's syndrome
Psychogenic:
Anxiety
Depression
Neurological:
Neuromuscular disorders
Physiological:
Obesity
Deconditioning
Others:
Trauma
Foreign body aspiration
Vocal cord dysfunction
Anaphylaxis

2.2.3 Evaluation of a Patient with Dyspnea

Dyspnea is a subjective multifactorial symptom that may be challenging to quantify. Physicians must be aware of the multiple factors influencing dyspnea that mimic clinical emergencies and include psychosocial distress. In the evaluation of a patient with dyspnea, there are clinical signs that should always be carefully analyzed and managed with emergency: hypotension, unstable arrhythmias, high respiratory rate (>40 breaths/minute), altered mental status, hypoxia, cyanosis, stridor, unsuccessful breathing effort, chest wall retractions, and tracheal deviation with unilateral breathing sounds (suggestive of pneumothorax) [1]. If these signs are present, a patient requires emergent management, including oxygen and consideration for ventilatory support [1].

Usually, patients with dyspnea may be categorized into two groups:

1. *Patients with comorbidities (cardiovascular, respiratory, or neuromuscular) with worsening of usual dyspnea*: In these patients, it is important to evaluate if there is a worsening and progression of the underlying disease and if there was a reversible factor contributing for the dyspnea. The best management usually involves the referral to a specialist physician to complete the study of the disease and optimize medical treatment [1].
2. *Patients with no comorbidities and new onset of dyspnea*: In these patients, the multiple causes of dyspnea have to be reviewed carefully. Clinical history and objective evaluation are the mainstays of diagnostic evaluation. In young patients, psychogenic dyspnea should be considered, especially if there is adequate oxygen saturation in room air, anxiety, tingling movements, and a good response to reassurance and acknowledgment of the underlying problem [1].

It is important to make a detailed evaluation of the patients, following these steps:

- *Personal background*: Patients should be asked about their medical history and medication. Cardiac and pulmonary diseases are mostly related to the cause of dyspnea. Also, it is important to characterize the onset of dyspnea, duration, associated pain, characteristics of that pain, relation with effort and factors contributing to exacerbation or relief. The presence of an exacerbated cough may suggest the exacerbation of a respiratory condition, or infection, especially if combined with worsening of sputum volume and purulence. The presence of a pleuritic chest pain (aggravates with cough and profound respiration) is suggestive of pericarditis, pneumonia, embolism, pneumothorax, and pleuritis. Angina represents a chest pain related to ischemic heart disease and is often accompanied by dyspnea and associated with a physical effort. Sudden dyspnea is suggestive of pneumothorax or pulmonary embolism. It is important to ask for the history of trauma, activities like scuba diving, that may precipitate a pneumothorax. Chronic dyspnea, with progressive worsening, may indicate congestive heart failure or worsening of chronic lung disease. Orthopnea (dyspnea in supine position) and paroxysmal nocturnal dyspnea (dyspnea while sleeping) may also be related with chronic heart failure or respiratory diseases. Smoking and other habits should be questioned. Other causes should be investigated, including gastroesophageal reflux and anxiety [1].
- *Physical examination:* At inspection, physicians should be alert to the respiratory effort of the patient with dyspnea, and look for signs of accessory muscles use and inability to speak due to dyspnea. Mental status may be impaired and should be assessed. Stridor is indicative of upper airway obstruction. The presence of neck veins distension may be present in cor pulmonale or cardiac tamponade. Also, thyroid size may be useful to evaluate, since thyroid dysfunction associates with dyspnea. Lower limbs with edema are common in patients with heart failure. Cyanosis or clubbing of upper extremities is suggestive of some chronic lung diseases. Ascites may be present and indicate chronic liver disease, and so hepatojugular reflux maneuver should be assessed [1].
- Pulsus paradoxus, the fall of at least 10 mmHg in blood pressure during inspiration, suggests chronic lung disease (COPD, asthma), cardiac tamponade, or pericardial constriction. Fever suggests infectious etiology [1].
- Chest wall palpation is important in the suspicion of pneumothorax, since subcutaneous emphysema may be present. Hyper-resonance at percussion is also suggestive of pneumothorax and dullness may indicate pulmonary consolidation or pleural effusion [1].
- A careful auscultation of lung and heart sounds is crucial. The absence of lung sound may indicate severe lung disease, pneumothorax, or pleural effusion; wheezing may indicate obstructive lung disease like asthma or COPD, although may also be present in pulmonary edema due to congestive heart failure. Dysrhythmic heart sounds may reveal unknown arrhythmia and a loud P2 may be present in pulmonary hypertension; reduced heart murmur may indicate heart failure or cardiac tamponade [1].
- *Complementary investigations in the acute setting*: Chest radiograph has great potential to aid in the diagnosis, since it allows a panoramic view of the lungs and may identify consolidations, pleural effusions, pneumothoraces, and other alterations. Electrocardiography may identify ischemic heart diseases, arrhythmias, and thromboembolic diseases. Blood tests including D-dimers (high sensitivity for pulmonary embolism), brain natriuretic peptide (BNP, high sensitivity for congestive heart failure) are also elemental in determining the cause, as well as blood gas tests. Lung and heart ultrasound may also be a quick tool to assess the cause of dyspnea in an emergency setting [1].
- *Complementary investigations in the outpatient setting*: Cardiopulmonary exercise testing and lung function tests are useful to identify the cause of dyspnea, especially when there are multiple comorbidities and causes for the dyspnea [1].

2.2.4 Measures of Dyspnea

Dyspnea is subjective and variable among patients, but it should be assessed by healthcare professionals and measured its intensity [1]. This assessment is useful for monitoring the efficacy of medical interventions [3]. Dyspnea may be assessed indirectly, for example, evaluating lung function and the severity of lung disease, or directly with quantification scales [3].

Some available clinical scales to quantify dyspnea are described:

- *Modified Medical Research Council (mMRC) Scale*: 5-point scale to quantify patients' sensation of breathlessness. Easy and practical to use, common in clinical daily practice and pulmonary rehabilitation (PR) [3];
- *Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI)*: Scales often used in PR to assess treatment outcome and daily-life activities limitation due to dyspnea. BDI is a discriminative tool, used as an initial baseline assessment in PR; TDI is a measure of change. Both analyze functional impairment, magnitude of task, and effort [3].

There are also psychosocial scales to characterize patients' dyspnea:

- *Rating of Perceived Exertion (RPE)*: Categorical scale to rate breathlessness with verbal descriptors (strong, weak, moderate intensity) associated with a score. 15 levels of assessment, from 6 to 20, due to close correlation with heart rate and workload (6 corresponds to 60 beats/minute; 20 corresponds to 200 beats/minute) [3];
- *10 Category-Ratio (CR 10)*: Categorical scale with 10 levels of breathlessness. In 1994 it was modified to application in respiratory patients, also known as Modified Borg Scale, widely used in PR programs [3]
- *Visual Analogue Scale (VAS)*: Represents a graphical scale of a continuum of dyspnea perception, with pictures or verbal descriptors of breathlessness. May be difficult to use at extremes of age (children and the elderly) [3].

Since severe dyspnea may have a significant impact in daily-life activities, subjective measures to quantify this impact have been described, and include: *London Chest Activity of Daily Living Scale* (LCADL), *Pulmonary Functional Status and Dyspnea Questionnaire* (PFSDQ), and *Oxygen Cost Diagram* (OCD) [3].

2.2.5 Management of Dyspnea

Management of dyspnea completely depends on the relief of symptoms, stabilization of patient's condition, and treatment of the underlying cause [1].

The main approaches may include:

- *Supplemental oxygen*: Oxygen is not indicated for the relief of breathlessness, but is useful for patients who are hypoxemic at rest, particularly those with chronic lung diseases [1].
- *Opioids*: Opioids have an important role in the relief of dyspnea. Short-term administration is useful in patients with advanced chronic lung and heart diseases. The usefulness of long-term administration of opioids remains controversial and should be considered on individual basis in patients with advanced disease [1].
- *Pulmonary rehabilitation (PR)*: PR is one of the best and most complete approaches to the treatment of chronic pulmonary patients with dyspnea, based mostly on exercise training and education to change behaviors and improve a healthy lifestyle. Studies demonstrate a reduction in exertional dyspnea, improved exercise capacity, and reduced breathlessness in daily-life activities [1].
- *Noninvasive ventilation (NIV)*: NIV reduces respiratory effort and ventilatory demand, therefore reducing dyspnea. It may be helpful in acute clinical setting (pulmonary edema, chronic lung disease exacerbation) or chronic [1].
- *Other approaches*: Other approaches may include a fan directed at a patient face, which has been documented to reduce breathlessness perception. It may be useful at rest or during PR [1].

2.2.6 Pathophysiology of Respiratory Failure

RF represents a condition with impairment of lung function and gas exchange, characterized by the decreased arterial partial pressure of oxygen ($PaO_2 < 60$ mmHg), hypoxemic RF or type I RF, and/or increased arterial partial pressure of carbon dioxide ($PaCO_2 > 45$ mmHg), hypercapnic RF or type II RF [2].

RF can be caused by two factors:

- *Lung failure*: Occurs due to respiratory infections (pneumonia) or disease (emphysema, interstitial disease, obstructive disease). Usually causes hypoxemic RF [2].
- *Pump failure*: The pump is constituted by the chest wall and respiratory muscles. Pump failure, also known as a ventilatory failure, may be caused by neuromuscular diseases or drug overdose with altered mental state. Usually causes hypercapnic RF [2].

Patients with multiple comorbidities may have both mechanisms contributing to RF. When both types coexist and hypoxemia is predominant, the situation is more dangerous than hypoventilation alone [2].

Patients with acute and chronic RF tend to adopt rapid shallow breathing, with increased respiratory frequency. Although the tidal volume decreases, ventilation/minute (V'E) remains constant or slightly increased and it prevents the fatigue of respiratory muscles, by decreasing the generated inspiratory effort. The mechanisms that cause this breathing pattern are not well understood, but it may represent a behavioral response to minimize breathlessness. However, its efficiency in terms of gas exchange is low [2].

The mechanisms of RF are linked. Lung impairment by respiratory diseases leads to increased work of breathing and energy demands. In a condition of hypoxemia, this generates muscle fatigue and ventilatory failure due to an imbalance between demanding and supplying of oxygen, which generates RF with hypercapnia. In patients with hypercapnia, usually there are clinical conditions that impair ventilatory function and also coughing capacity, which leads to secretions clearance impairment, respiratory infections, and lung atelectasis. These conditions are responsible for ventilation/perfusion mismatch, a mechanism that generates hypoxemia [2].

2.2.7 Type I Respiratory Failure

Type I RF, or hypoxemic RF, characterizes by decreased arterial oxygen tension ($PaO_2 < 60$ mmHg) [2].

The main causes are:

- *Ventilation/perfusion mismatching*: Occurs in COPD exacerbation, pulmonary embolic disease [4].
- *Shunt*: Mechanism that occurs in pneumonia, atelectasis, pulmonary edema, patent foramen ovale, congenital heart diseases, vascular malformations [4].
- *Diffusion impairment*: Occurs in idiopathic pulmonary fibrosis (IPF) [4].
- *Alveolar hypoventilation*: Occurs due to narcotic overdose, head injury, airway obstruction, neuromuscular disorders [4].
- *Low inspired oxygen*: Occurs due to high altitude [4].

2.2.8 Type II Respiratory Failure

Type II RF, or hypercapnic respiratory failure, is characterized by increased arterial carbon dioxide tension ($PaCO_2 > 45$ mmHg) [2]. The main causes are:

- *Increased production of CO_2*: In a steady state, the amount of CO_2 production ($V'CO_2$) is ~200 ml/min, and the same amount is eliminated. States of hyperthermia, including physical exercise or fever, increase the production of CO_2 by ~14% for each Celsius degree rise. In normal conditions, the increase in CO_2 stimulates the CNS to increase V'E, to maintain $PaCO_2$ stable. However, in conditions of impaired ventilatory function, this response does not occur, and type II RF develops [2].

- *Alveolar hypoventilation*: Alveolar ventilation may be impaired by conditions that decrease the respiratory frequency, tidal volume or total ventilation and contribute to hypercapnia [2].
- *Pump failure*: This mechanism occurs when there is inadequate output from CNS to peripheral respiratory muscles due to anesthesia, drug overdose, medulla diseases, when there is impairment of the chest wall due to trauma, kyphoscoliosis, neuromuscular diseases or severe hyperinflation in chronic obstructive pulmonary diseases, or when there is respiratory muscle fatigue, which may also happen in neuromuscular conditions, where respiratory muscles are weakened [2].
- *Pulmonary hyperinflation*: Pulmonary hyperinflation corresponds to a condition where end-expiratory lung volume is increased. Chronic obstructive lung diseases predispose to this condition. Pulmonary hyperinflation impairs respiratory function by shortening respiratory muscle fibers and demanding more energy to their contraction, more generated pressure, thus increasing the work of breathing. Also, diaphragmatic contraction is impaired and its contribution to ventilation is minimized. These conditions contribute to increasing respiratory muscle fatigue and impaired ventilation, thus leading to hypercapnia [2].

2.2.9 Acute Respiratory Failure

Acute respiratory failure (ARF) is a frequent medical condition in emergency care, with high morbidity and mortality. Usually, it results from an impairment in the respiratory system, either affecting the respiratory pump, the lung, or even both [5]. COPD exacerbations are a frequent cause of ARF, either hypoxemic and/or hypercapnic, and patients' in-hospital mortality reach 2–8%, and up to 15% in ICU [5].

Hypoxemic ARF is frequent in an emergency context. In the USA, this accounts for a hospital mortality up to 20%. Main identifiable causes are pneumonia, heart failure with pulmonary edema, acute respiratory distress syndrome (ARDS), and COPD exacerbation [4]. Chest trauma may also contribute to hypoxemia [5]. ARDS is a frequent cause of hypoxemic ARF and it is characterized by an acute inflammatory injury of the lungs, with increased vascular permeability and loss of aerated lung tissue. ARDS may present in the severe form (arterial partial pressure of oxygen/fraction of inspired oxygen [PaO_2/FiO_2] <100 mmHg) and have in-hospital mortality up to 42% [5].

Hypercapnic ARF may occur in the context of anatomical and functional defects of CNS, neuromuscular diseases, defects of the ribcage, and other conditions leading to respiratory muscles fatigue. Drug overdose, infections, and trauma may lead to impaired ventilation and consequently type II RF. These conditions lead to a decrease in tidal volume, which is compensated by an increase in respiratory frequency in order to maintain V'E constant (rapid and shallow breathing). However, this response has poor efficacy in terms of gas exchange and hypercapnia develops. Due to fatigue, inspiratory time increases as respiratory frequency and V'E decrease. CNS adapts to this condition decreasing output signals and respiratory arrest occurs [2].

In conditions of pulmonary edema (ARDS or heart failure) the patient is hyperventilating and energy demands are high; however, energy supply is impaired due to hypoxemia and/or low cardiac output, leading to respiratory failure. Also, weaning from invasive ventilation (IV) may lead to respiratory muscles fatigue and type II ARF [2].

The causes of ARF are evidenced in Table 2.2.

Patients often present with acute-on-chronic RF due to a deterioration of their chronic condition. This is usually seen in patients with exacerbation of COPD due to a respiratory infection, and patients present with increased dyspnea. This aggravates their hyperinflation and intrinsic positive end-expiratory pressure (PEEPi), which is

Table 2.2 Possible causes for the development of respiratory failure [2, 4, 6]

Causes of respiratory failure
Acute respiratory failure:
Hypoxemic:
Pneumonia
ARDS
Heart failure
COPD exacerbation
Trauma
Hypercapnic:
Drugs
Poisoning
Encephalitis
Sepsis
Circulatory shock
Stroke
Trauma
Tetanus
Neuromuscular diseases
Acute hyperinflation
Obstructive lung diseases
Pulmonary edema
Prematurity
Weaning from noninvasive ventilation
Chronic respiratory failure:
Hypoxemic:
Pulmonary hypertension
COPD
Pulmonary thromboembolism
Heart failure
Lung cancer
Obstructive sleep apnea
Small airway diseases
Interstitial lung diseases
Hypercapnic:
Chronic obstructive lung diseases
Chest wall abnormalities
Obesity
Thoracoplasty
Pleural effusion
Neuromuscular diseases
Systemic diseases (scleroderma, polymyositis, systemic lupus)
Primary alveolar hypoventilation (Ondine's disease)
Electrolyte abnormalities
Malnutrition
Endocrine disorders

responsible for increasing the work of breathing and consequently generating hypercapnic RF [2].

2.2.10 Chronic Respiratory Failure

There are many etiologies for the development of chronic respiratory failure (CRF). Its correct identification is crucial for adequate management and treatment. The most common causes of CRF, particularly hypoxemic, are pulmonary hypertension, COPD, pulmonary thromboembolism, heart failure, lung cancer, obstructive sleep apnea, small airway, and interstitial lung diseases [6].

Chronic RF2 is seen more often in patients with COPD, although the mechanisms behind its pathophysiology are not yet completely understood. COPD patients with hypercapnia tend to adopt the mechanism of rapid shallow breathing, when compared with other COPD patients. The likelihood of developing RF2 is higher in patients with more hyperinflation. Chronic modifications in the CNS lead to decreased efferent output signaling and impaired ventilation, through mechanisms still unknown [2].

The causes of chronic respiratory failure are evidenced in Table 2.2.

2.2.11 Evaluation of Respiratory Failure

Patients with RF require peripheral oxygen saturation assessment or a blood gas test (gasometry).

Thoracic imaging with radiograph or CT scans is fundamental to evaluate lung, cardiovascular, and chest structural abnormalities. Blood tests with hemogram, D-dimers, BNP, and biochemistry parameters may help identify or exclude many etiologies [6].

Other useful complementary studies include pulmonary function tests, electrocardiography, echocardiography, cardiopulmonary exercise tests, 6-min walk or shuttle walk tests. Sleep

studies should be performed in the suspicion of sleep disorders [6].

2.2.12 Management of Respiratory Failure

Management of respiratory failure depends on the cause and the setting where it occurs.

Treatment of acute respiratory failure treatment may include:

- Treating respiratory infections [7].
- Bronchodilators and corticosteroids are particularly important in chronic obstructive pulmonary diseases and help reverse impaired lung mechanics [7].
- Supplemental oxygen (conventional nasal cannula or high-flow nasal cannula) [4].
- Treat sedatives/opioids intoxication with flumazenil or naloxone, respectively [7].

NIV in cases of acute exacerbation of COPD with acidosis (pH < 7.35), cardiogenic pulmonary edema (NIV or continuous positive airway pressure [CPAP]), immunocompromised patients, post-operative, palliative care, chest trauma, to prevent post-extubating respiratory failure in high-risk patients and to facilitate weaning from IV in patients with hypercapnic RF [7, 8]. NIV is helpful in the treatment of either acute or chronic RF [7].

Prevention of ARF includes vaccination, adherence to pharmacological treatment, and adoption of a healthy lifestyle [7].

2.3 Conclusion Discussion

Dyspnea is a common symptom, often distressing and a motive for hospital admission. It is a subjective experience, highly variable, multifactorial, and sometimes difficult to assess. It may have an acute or chronic onset. The main causes are lung and/or heart diseases. These conditions often predispose to the development of respiratory failure, either hypoxemic and/or hypercapnic. The best management includes the relief of symptoms and treatment of the underlying cause.

Key Major Recommendations

- Dyspnea is a subjective multifactorial and complex symptom.
- Dyspnea is a common symptom, often distressing and a motive for hospital admission.
- Many causes of dyspnea lead to the development of respiratory failure.
- Respiratory failure may have acute or chronic onset, and be hypoxemic and/or hypercapnic.
- Management of dyspnea and respiratory failure includes the relief of symptoms and treatment of the underlying cause.

References

1. Coccia C, Palkowski G, Schweitzer B, et al. Dyspnoea: pathophysiology and a clinical approach. SAMJ. 2016;106(1):32–6.
2. Roussos C, Koutsoukou A. Respiratory failure. Eur Resp J. 2003;22(47):3s–14s.
3. Crisafulli E, Clini E. Measures of dyspnea in pulmonary rehabilitation. Multidiscip Respir Med. 2010;5(3):202–10.
4. Kapil S, Wilson J. Mechanical ventilation in hypoxemic respiratory failure. Emerg Med Clin N Am. 2019;37:431–44.
5. Scala R, Heunks L. Highlights in acute respiratory failure. Eur Resp Rev. 2018;27:180008.
6. Faverio P, Giacomi F, Bonaiti G, et al. Management of chronic respiratory failure in interstitial lung diseases: overview and clinical insights. Int J Med Sci. 2019;16(7):967–80.
7. Calverley P. Respiratory failure in chronic obstructive pulmonary disease. Eur Respir J. 2003;22(47):26s–30s.
8. Rochwerg B, Brochard L, Elliott M, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Resp J. 2017;50:1602426.

Part II

Noninvasive Ventilation: Pulmonary Function Measurements—Classification, Screening Test and Questionnaires

Diaphragm Function. Pulmonary Function Testing

3

Serafeim Chrysovalantis Kotoulas, Athanasia Pataka, and Vasileios Voutsas

Abstract

Noninvasive ventilation (NIV) has been established in the last decades as an alternative to invasive mechanical ventilation, with better results in many cases. This chapter analyses the effects of NIV in diaphragmatic function and pulmonary function tests by investigating the action mechanisms of NIV in diseases that cause diaphragmatic dysfunction or compromise pulmonary function and deteriorate pulmonary function tests (PFTs).

Keywords

Diaphragm · Pulmonary function tests · Functional status · Noninvasive ventilation

Abbreviations

ABG	Arterial blood gas
ALS	Amyotrophic lateral sclerosis
ARDS	Acute respiratory distress syndrome
C3–C5	Cervical segments three, four, and five
COPD	Chronic obstructive pulmonary disease
CPAP	*Continuous positive airway pressure*
DLCO	*Diffusion capacity of the lung for carbon monoxide*
ERV	Expiratory reserve volume
FEV1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
FVC	Forced vital capacity
IC	Inspiratory capacity
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
IRV	Inspiratory reserve volume
MV	Minute ventilation
NIV	Noninvasive ventilation
PaCO2	*Partial pressure of carbon dioxide*
PEEP	*Positive end expiratory pressure*
PEEPi	Intrinsic positive end expiratory pressure
PFTs	Pulmonary function tests
PS	Pressure support
RR	Respiratory rate
RV	Residual volume
SNIP	Sniff nasal inspiratory pressure
TLC	Total lung capacity
twitch Pdi	Bilateral transcutaneous phrenic nerve stimulation

S. C. Kotoulas (✉) · V. Voutsas
1st ICU, G. Papanikolaou Hospital
Thessaloniki, Greece

A. Pataka
Pulmonary Medicine, Respiratory Failure Unit,
G. Papanikolaou Hospital, Thessaloniki, Greece

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_3

VC	Vital capacity
VO_2 max	*Maximal oxygen consumption*
Vt	Tidal volume

3.1 Introduction

Diaphragm is the most important muscle of inspiration. It consists of a thin sheet of muscle fibers which are inserted into the lower ribs forming a muscle with a dome-like shape. The diaphragm is supplied by the phrenic nerves from cervical segments three, four, and five (C3–C5). Its contraction forces abdominal contents downward and forward and increases the vertical and the transverse dimension of the chest cavity. During normal tidal breathing, the diaphragm moves about 1 cm, while on forced inspiration this movement can be extended up to 10 cm [1]. Imaging tests and especially ultrasound can be used to assess diaphragm function. The gold standard measurement of diaphragmatic strength is transdiaphragmatic pressures during unilateral and bilateral transcutaneous phrenic nerve stimulation (twitch Pdi); however, sniff nasal inspiratory pressure (SNIP) measurement is more useful due to being easier to perform in everyday clinical practice and therefore is more widely used. Diaphragm dysfunction is associated with dysphea, intolerance to exercise, sleep disorders, hypoventilation with daytime hypercapnia, and a potential impact on survival. SNIP measurements more negative than −45 mmHg exclude clinically important respiratory muscle weakness, while measurements less negative than −30 mmHg are predictive of significant nocturnal hypoxia [2]. Yet, another widely used way to measure respiratory muscle strength is maximal inspiratory and expiratory pressures (Fig. 3.1). Noninvasive ventilation (NIV) is used as an effective long-term treatment in many diseases with chronic compromisation of the diaphragm function. In critical conditions, acute diaphragmatic fatigue usually leads to rapid respiratory arrest. In such cases, NIV is also effective in delaying or even preventing that by reinforcing diaphragmatic function.

Pulmonary function tests (PFTs) are the key measurements for the assessment of lung function. Some of the basic parameters of lung function, such as forced expiratory volume in 1 s (FEV1), tidal volume (Vt) and vital capacity, and forced vital capacity (VC and FVC), can be measured with a simple spirometer (Fig. 3.2) [2]. Expiratory reserve volume (ERV), inspiratory reserve volume (IRV), and inspiratory capacity (IC) can also be measured with a classic spirometer, while gas dilution technique or body plethysmograph are necessary for the measurement of functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC) (Fig. 3.3) [2]. Based on PFTs, there are two major pathological lung function patterns, obstructive and restrictive pattern. Obstructive pattern is defined as an FEV1/FVC ratio lower than 0.7, while restrictive pattern as a TLC value below 80% of the predicted value. Patients with both disorders have a mixed pattern defect. Apart from FEV1/FVC ratio and TLC, all measurements can be affected in lung diseases. Patients with an

Fig. 3.1 A portable machine for the measurement of maximal inspiratory and expiratory pressures

Fig. 3.2 A person performing simple spirometry

Fig. 3.3 A body plethysmograph

obstructive pattern defect usually present increased lung volumes (RV, FRC, TLC), because of air trapping, and decreased FEV1, ERV, and IC with varying FVC. On the other hand, patients with restrictive pattern defect usually present decreased lung volumes and capacities [2]. NIV can be used in both acute and chronic conditions in patients with diseases which are presented with either an obstructive or restrictive lung function pattern, as well as in patients with mixed pattern defect. In such cases, the use of NIV can improve lung function, something that is reflected in the improvement of PFTs' measurement results.

3.2 Discussion and Analysis of the Main Topic

The diaphragm is the main respiratory muscle accounting for approximately 70% of the work of breathing in normal subjects. Diaphragmatic dysfunction plays a key role in respiratory failure. There are numerous conditions that could cause diaphragmatic dysfunction such as (1) neuropathies, (2) myopathies, (3) metabolic abnormalities, (4) decreased oxygen delivery, (5) medications, etc. [3]. Moreover, there is well-established evidence for diaphragmatic dysfunction due to mechanical ventilation both in animals and in critically ill patients. The mechanisms which are responsible for mechanical ventilation-induced diaphragmatic dysfunction are: (1) diaphragmatic injury due to excessive respiratory muscle loading, (2) hypercapnia under controlled ventilation, and (3) disuse atrophy secondary to diaphragm inactivity from excessive ventilatory support [3]. In order to prevent that, the ventilator could be theoretically set in an optimal way, so that a clinically acceptable level of work of breathing could be targeted. Apart from invasive mechanical ventilation, this could also be applied with NIV. Vivier et al. [4] evaluated the magnitude of diaphragmatic work by using diaphragmatic ultrasound (Envisor system; Philips ultrasound; Bothell, WA, USA) hypothesizing that the diaphragm's thickness in its zone of

apposition could reflect the magnitude of diaphragmatic work and could help clinicians to optimize ventilator settings. They measured diaphragm thickness at the end of inspiration and at the end of expiration and calculated the thickening fraction. They also used a pneumotachograph (Fleisch N°2; Fleisch; Lausanne, Switzerland) to measure air flow and a double-balloon catheter (Marquat; Boissy Saint Le'ger, France) to measure esophageal and gastric pressures and they obtained the transdiaphragmatic pressure and the transdiaphragmatic pressure–time product per breath by measuring the area under the transdiaphragmatic pressure signal from the onset of its positive deflection to its return to baseline. They performed these measurements in intensive care unit (ICU) patients during spontaneous breathing and during three NIV periods with increasing pressure support (PS). They found that increasing PS was associated with decreased transdiaphragmatic pressure–time product and thickening fraction and that transdiaphragmatic pressure–time product was significantly correlated with thickening fraction, but not with expired tidal volume, while the directional changes in thickening fraction after a change in the PS level followed reasonably those in transdiaphragmatic pressure–time product with a significant correlation coefficient. Since thickening fraction values did not correlate with expired tidal volume, thickening of the diaphragm reflected muscle effort and not the increase in pulmonary volume induced by ventilation [4]. Those highly reproducible findings indicate that NIV could be used to help clinicians to optimize the magnitude of ventilator support to target a clinically acceptable level of work of breathing and prevent ventilation-induced diaphragmatic dysfunction. The correlation between the transdiaphragmatic pressure–time product and the diaphragmatic thickening fraction in this research also points out that bedside ultrasonography can reliably replace diaphragm electromyography, measurement of pleural or esophageal and gastric pressures, and derived variables such as work of breathing as a simple and accurate method to assess diaphragmatic performance in the ICU. This may help identifying patients with diaphragmatic dysfunction during weaning from invasive mechanical ventilation making them suitable candidates for NIV.

In obstructive lung diseases, mainly chronic obstructive pulmonary disease (COPD)—emphysema and in increasing age in a lesser degree, changes in pulmonary elastic properties with decreased elastic recoil and increased compliance end up in dynamic hyperinflation, which can become extremely severe, and favor volume overload, resulting in diaphragmatic dysfunction due to mechanical causes. Indeed, in patients with COPD with frequent exacerbations the maximum pressure produced by the diaphragm's contraction is significantly lower than in individuals without COPD, a fact explained by the diaphragmatic shortening and the mechanical derangement following onset of progressive lung hyperinflation. In addition to that, in COPD exacerbation the intrinsic positive end expiratory pressure (PEEPi) due to the collapse of the small airways and the subsequent air trapping behaves as an additional load that the diaphragm has to overcome in order to generate inspiratory flow. Under these circumstances, the diaphragm soon exhausts its functional reserve, and subsequently mechanical impairment occurs. Marchioni et al. [5] assessed diaphragmatic function in patients with acute exacerbation of COPD who received NIV by a high-performance ventilator (Engström Carestation; GE Healthcare Life Sciences; Helsinki, Finland) via a face mask (Philips Respironics; Murrysville, PA, USA) in a respiratory ICU, setting inspiratory positive airway pressure (IPAP) so that to achieve specific Vt, respiratory rate (RR), minute ventilation (MV), and waveforms according to recommendations. Diaphragm function was assessed both with bedside ultrasound (GE Vivid 7; GE Healthcare; Little Chalfont, UK) by measuring the change in diaphragm thickness in the zone of apposition during the respiratory cycle with the patient in supine position with an average inclination of 45 degrees and with inflatable balloon catheters (NutriVent® nasogastric polyfunctional catheter; SIDAM; Mirandola, Italy) by measuring the transdiaphragmatic generating pressure capacity obtained through a sniff maneuver starting at FRC. Diaphragm dysfunction was defined as a

bilateral change in diaphragm thickness in the zone of apposition less than 20%. Patients with diaphragm dysfunction had significantly lower transdiaphragmatic generating pressure capacity and a significantly higher risk for NIV failure compared with patients without diaphragm dysfunction. A change in diaphragm thickness in the zone of apposition less than 20% predicted more accurately NIV failure than arterial blood gas (ABG) baseline pH and partial pressure of carbon dioxide (PaCO2) and pH changes within 2 h after NIV was started, while it demonstrated the same accuracy with transdiaphragmatic generating pressure capacity obtained through a sniff maneuver in identifying diaphragm dysfunction [5]. These findings suggest that the early and noninvasive assessment of diaphragmatic dysfunction during severe COPD exacerbation requiring NIV seems accurate and helpful in predicting NIV failure and avoiding the risk of delayed intubation. Furthermore, it indicates that the use of NIV in an acute COPD exacerbation might be more capable in improving lung mechanics by implementing positive end expiratory pressure (PEEP), which antagonizes PEEPi, ameliorates small airway collapse, and reduces air trapping and hyperinflation, than in reinforcing diaphragm function. Nevertheless, the successful implementation of NIV in cases of patients with evident diaphragmatic dysfunction demonstrates that apart from lung mechanics, NIV is also useful in supporting diaphragm function compromised by mechanical causes due to lung hyperinflation.

Post-surgery acute respiratory failure mainly develops following abdominal or thoracic surgery. The risk for post-operative pulmonary complications increases with patient-related risk factors such as age older than 60 years, COPD, obesity, functional dependence, and congestive heart failure. The use of anesthesia and post-operative pain induce hypoxemia, atelectasis, decreased pulmonary volumes, and diaphragm dysfunction. Jaber et al. [6] reviewed the effects of NIV on post-operative respiratory function and on the management and prevention of post-operative respiratory failure. Imaging studies showed that NIV may increase lung ventilation and decrease the amount of atelectasis during the post-operative period in patients undergoing major abdominal surgery, a fact that could be attributed to the enforcement of the diaphragm function. In obese patients with restrictive respiratory disorder undergoing gastroplasty, nasal NIV during the post-operative period improved the diaphragm dysfunction and accelerated recovery of patients [6]. Furthermore, NIV has been shown to improve post-operative gas exchange and cardiac index. This results in better tissue perfusion and oxygenation and less carbon dioxide retention. For diaphragm particularly, this process improves myocyte function and diaphragm function in general. All of the above resulted in a lower percentage of patients with acute respiratory failure after abdominal or thoracic surgery, lower rates of reintubation, acute respiratory distress syndrome (ARDS) and anastomosis leakage, shorter length of ICU stay, reduction in hospital length of stay, and mortality. In addition to that, some of the beneficial properties of NIV were also observed with combined prophylactic usage in the pre-operative and post-operative period, mainly depending on the underlying disease of patients rather than the post-operative respiratory complications [6].

Neuromuscular disorders such as Guillain–Barré syndrome, amyotrophic lateral sclerosis (ALS), critical illness neuromyopathy, poliomyelitis, spinal cord injury, phrenic nerve trauma, myasthenia gravis, Eaton-Lambert syndrome, Duchenne muscular dystrophy, inflammatory myopathies (e.g., polymyositis and dermatomyositis), thyroid myopathy, and metabolic myopathies usually progress in respiratory failure due to respiratory muscle insufficiency. Diaphragm plays a major role in this process, since it is responsible for approximately 70% of the work of breathing in normal subjects. Clinical features of such conditions could be sleep-disordered breathing (morning headache, daytime sleepiness, disrupted sleep pattern, impaired intellectual function), breathlessness, orthopnea, and poor cough. There are many tests of respiratory muscle function that are used in the diagnosis and follow up of these conditions. The value of sleep studies has been recognized the last decades in

these conditions since nocturnal hypoventilation is one of the initial dysfunctions that accompanies them. Overnight oximetry and capnometry constitute an essential part of the assessment for the early detection of nocturnal hypoventilation. Although some investigators support the use of polysomnography to confirm and quantify arousals during respiratory events, nocturnal hypoventilation can be managed simply with overnight titration of NIV to a defined level of hypercapnia, irrespective of the sleep stage of the patient. With disease progression, NIV is an integral part of patient management even at daytime as it can support diaphragm function and prevent respiratory muscle fatigue. In incurable conditions, the only choice to continue patient support would be tracheostomy and invasive mechanical ventilation, which however carries substantial side effects and is related with poor outcomes in long-term survival [7].

The performance of PFTs is the cornerstone of the assessment of respiratory system in healthy subjects and in patients with thoracic and other diseases. The most important and most often used measurement is that of FEV1. In many studies, especially those concerning obstructive lung diseases, FEV1 is used as a primary or a secondary endpoint to assess clinical results after an intervention such as the use of a medication or the use of NIV. NIV can be used as a chronic treatment in end-stage respiratory diseases or as a treatment in the acute phase of an exacerbation of such diseases. COPD and cystic fibrosis are characteristic examples of respiratory diseases, in which NIV has been used successfully in their chronic management. Budweiser et al. [8] retrospectively assessed 46 patients with stable COPD undergoing NIV treatment after exhaustion of all available medical treatment (all patients had received β-agonists, anticholinergic agents, theophylline, inhaled steroids, and on occasion systemic steroids) in 6 and 12 months after NIV treatment initiation. NIV was administered through a nasal or full facemask of different sizes and types (nasal mask Gold or Special; Respironics Inc.; Murrysville, PA, USA, and NV ultramirage nasal or fullface mask; ResMed Inc.; North Ryde, Australia) or, if necessary, via an individually manufactured mask with four different home respirators, most often the Onyx plus (Nellcor Puritan Bennett Inc.; Courtaboef Cedex, France) or the BIPAP synchrony ST (Respironics Inc.; Murrysville, PA, USA). NIV was set in the spontaneous-timed (assist-controlled) mode with low inspiratory pressure and back-up respiratory frequency and after a phase of adaption the ventilation parameters were increased to the patient's comfort level, targeting a tidal volume of 7–10 ml/kg, while oxygen was supplemented as required to achieve an oxygen saturation of more than 90%. In case of a persistent hypercapnia, the inspiratory pressure was increased in order to achieve more effective ventilation. PFTs were performed using a whole-body plethysmography (Masterlab; Jaeger Inc.; Würzburg, Germany) following the guidelines of the American Thoracic Society, based on the reference values of the European Community for Steel and Coal. They found that FEV1, VC, and IC were significantly improved after treatment with NIV. RV/TLC ratio was also significantly improved after 6 and 12 months of NIV treatment, while for the patients with the most severe hyperinflation (RV/TLC > 75%), a significant positive correlation between IPAP and the reduction in RV/TLC ratio was also found. These findings suggest that in stable COPD the use of long-term NIV treatment can decrease hyperinflation, thereby improving inspiratory capacity. This reduction in hyperinflation was also accompanied by a significant and sustained reduction in PaCO2. This improvement could be explained by the changes in ventilatory pattern with the decreased respiratory frequency and the augmented Vt, the decrease of RV and PEEPi, the reduction in the frequency or severity of exacerbations and the beneficial mucous clearance [8]. Apart from COPD, the chronic use of NIV has been also shown to improve PFTs, mainly FEV1, in cystic fibrosis, which is another obstructive pulmonary disease, by improving the same disease parameters as in COPD.

Acute exacerbations are manifestations of obstructive lung diseases and NIV is a very important treatment option for these life-threatening events. During an acute exacerbation of an obstructive lung disease, airway obstruction

becomes critical, resulting in small airway collapse, air trapping, lung hyperinflation, and increased PEEPi, while the increased volume of bronchial secretion deteriorates the problem. Dwyer et al. [9] randomly selected 40 adults with moderate to severe cystic fibrosis lung disease who were admitted to hospital for an acute exacerbation, with an FEV1 < 60% of the predicted value at admission, and assessed the use of NIV in the clinical outcomes of the acute exacerbation in a randomized controlled clinical trial setting. They divided their participants into two different groups: the control group which received standard comprehensive inpatient care, which included the active cycle of breathing technique, manual percussion, vibration, postural drainage positioning, autogenic drainage, positive expiratory pressure and oscillating positive expiratory pressure, and the experimental group which received the same care with the addition of NIV during airway clearance treatments from day 2 of admission until discharge. Among other findings, which included significantly less fatigue, reduced sputum bacterial load and increased respiratory muscle strength, the patients of the experimental group exhibited a significantly higher FEV1 (%predicted) at discharge compared to the control group [9]. These findings indicate that NIV is an effective treatment intervention during an acute exacerbation of an obstructive lung disease, not only due to the improvement of lung mechanics, air trapping, hyperinflation, and PEEPi, as discussed previously, but also due to the improvement of bronchial secretion clearance. Furthermore, the preservation of respiratory muscle strength with chest physiotherapy for those using NIV seems to intensify NIV effectiveness in improving lung mechanics. The combination of all these mechanisms of action results in a significant improvement in PFTs and particularly FEV1, which is a key index for the assessment of a treatment intervention. Similar findings have also been reported in studies of COPD acute exacerbations, indicating common action pathways of NIV in the acute exacerbations of obstructive lung diseases.

Apart from obstructive pulmonary diseases, NIV is also useful in patients with restrictive pulmonary diseases. Conditions such as cardiogenic pulmonary edema, obesity hypoventilation syndrome, pulmonary infections mainly in immunocompromised patients and post-surgery atelectasis are examples of both acute and chronic restrictive pulmonary diseases in which NIV can play a role in their management by improving lung mechanics. In patients with cardiogenic pulmonary edema which is a consequence of heart failure, alveoli get filled with fluid and regional atelectasis are emerged resulting in decreased FRC and lung compliance and in type I respiratory failure. In such cases, NIV can improve lung mechanics by increasing FRC with the implementation of PEEP, which can also be done with continuous positive airway pressure (CPAP). Nevertheless, compared to CPAP, NIV has the advantage to be effective in patients with cardiogenic pulmonary edema exhibiting hypercapnia by enforcing respiratory muscle strength. NIV can also be effective in cases of pulmonary infection, especially in immunocompromised patients. It has been shown that in these cases, when NIV is applied early, it can significantly ameliorate the respiratory symptoms of these patients and reduce the need for intubation and overall mortality. NIV improves lung mechanics in these patients by improving FRC with the same mechanism as in patients with cardiogenic pulmonary edema. On the contrary, NIV has not exhibited the same effectiveness in improving the outcomes in immunocompetent patients with lung infection, with the exception of the subgroup of patients with COPD. It seems that in these cases, when the infection is localized and there is no preexisting lung pathology, the implementation of NIV does not improve lung mechanics. NIV has also been shown to be effective in cases of major surgery, complicated by the occurrence of atelectasis and pneumonia. In such cases NIV can prevent the occurrence of atelectasis, resulting in larger lung volumes and better lung mechanics with increased FRC. Another restrictive respiratory disease in which NIV has been shown to be effective is obesity hypoventilation syndrome. In this syndrome, the implementation of NIV is chronic and improves clinical outcomes by

improving lung mechanics and by enforcing the function of respiratory pump [7]. Respiratory morbidity due to neuromuscular disorders is caused mainly due to diaphragmatic dysfunction. Nevertheless, lung compliance has also been found to decrease in patients with neuromuscular disorders compared to healthy subjects. Lechtzin et al. [10] assessed lung compliance, in patients with ALS and in healthy volunteers, before and right after the appliance of positive pressure ventilation, administered via a mouthpiece. ALS patients presented significantly lower baseline lung compliance compared to healthy volunteers; however, their lung compliance was increased significantly after positive pressure ventilation, something that was not observed in healthy volunteers [10]. These findings suggest that, apart from diaphragmatic dysfunction, patients with neuromuscular disorders also present disrupted pulmonary function, probably due to atelectasis or increased alveolar surface forces, which are improved with positive pressure ventilation, mainly due to the improvement of FRC.

Another useful application of NIV is in patients with lung cancer that are going to be subjected to surgery. The capability of a patient to be subjected to surgical resection of a lung tumor and the size of the part of the lung that is going to be resected (segmentectomy, lobectomy, *and pneumonectomy) are dependent by the pre-operational functional status of the patient, which can be assessed by the PFTs and more particularly by the FEV1, the diffusion capacity of the lung for carbon monoxide (DLCO), and the maximal oxygen consumption (*VO_2 *max). There are different thresholds of pre-operative predicted values for these parameters which correspond to the different sizes of lung tissue that are allowed to be resected. Bagan* et al. [11*] assessed 20 consecutive patients with a clinical N0 non-small cell lung cancer, in whom the predicted post-operative respiratory function (FEV1 and* VO_2 *max) was below the guideline thresholds for eligibility for surgical resection and/or associated with severe co-morbidities. They subjected them into a cardiorespiratory rehabilitation program and 3 h of NIV each day and they repeated their functional tests after 3 weeks of therapy. They found that the patients displayed a significant increase in their FEV1 and* VO_2 *max, which allowed surgical resection to go ahead in all patients, with low percentage of morbidity and mortality, while further postoperative rehabilitation allowed a return at home almost all the patients* [11*]. These findings suggest that a pulmonary rehabilitation program together with the use of NIV allows surgery to be performed in patients who are not initially eligible for resection.*

3.3 Conclusion Discussion

Compared to invasive mechanical ventilation, NIV has shown to be effective in preventing ventilation-induced diaphragmatic dysfunction by targeting a clinically acceptable level of work of breathing to optimize the magnitude of ventilator support. NIV has also been proved to be useful in supporting diaphragm function when it is compromised both by mechanical causes due to lung hyperinflation and by a thoracic or an abdominal surgery, while it is the treatment of choice at the early stages of neuromuscular disorders, when the only symptom is nocturnal hypoventilation due to diaphragmatic dysfunction.

Apart from diaphragmatic function, NIV can effectively improve pulmonary function in patients with obstructive lung diseases, both after chronic use, by increasing FEV1 and decreasing RV/TLC, and in the phase of an acute exacerbation. NIV is also effective in restrictive lung diseases and in neuromuscular disorders that cause respiratory morbidity, mainly by increasing FRC, while it can improve lung function in patients with lung cancer before a resection surgery, so that they could withstand the surgery and avoid post-operative complications.

Key Major Recommendations

- In patients who suffer from diseases that cause diaphragmatic dysfunction or compromise pulmonary function and necessitate ventilatory support, try NIV first, especially in cases such as COPD exacerbation, pulmo-

nary edema, or pulmonary infection in immunocompromised, where NIV improves survival compared to invasive mechanical ventilation.

- When applying PEEP target a value which provides the optimal FRC and lung compliance.
- When applying IPAP target a value which provides the optimal RR and Vt and restrain hypercarbia and respiratory acidosis.

References

1. West JB, Luks AM. West's respiratory physiology the essentials. 10th ed. Philadelphia, PA: Wolters Kluwer Yearbook; 2016. p. 109.
2. Dakin J, Mottershaw M, Kourteli E. Making sense of lung function tests a hands-on guide. 2nd ed. Danvers, MA: CRC Press Taylor & Francis Group Yearbook; 2017. p. 13–28, 57–63, 90–95
3. Dres M, Goligher EC, Heunks LMA, et al. Critical illness-associated diaphragm weakness. Intensive Care Med. 2017;43:1441–52.
4. Vivier E, Mekontso Dessap A, Dimassi S, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med. 2012;38:796–803.
5. Marchioni A, Castaniere I, Tonelli R, et al. Ultrasound-assessed diaphragmatic impairment is a predictor of outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease undergoing noninvasive ventilation. Crit Care. 2018;22:109.
6. Jaber S, De Jong A, Castagnoli A, et al. Non-invasive ventilation after surgery. Ann Fr Anesth Reanim. 2014;33:487–91.
7. Spiro SG, Silvestri GA, Agusti A. Clinical respiratory medicine. 4th ed. Philadelphia, PA: Elsevier Saunders Yearbook; 2012. p. 432–3, 763–768
8. Budweiser S, Heinemann F, Fischer W, et al. Long-term reduction of hyperinflation in stable COPD by non-invasive nocturnal home ventilation. Respir Med. 2005;99:976–84.
9. Dwyer TJ, Robbins L, Kelly P, et al. Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial. J Physiother. 2015;61:142–7.
10. Lechtzin N, Shade D, Clawson L, et al. Supramaximal inflation improves lung compliance in subjects with amyotrophic lateral sclerosis. Chest. 2006;129:1322–9.
11. Bagan P, Oltean V, Ben Abdesselam A, et al. Pulmonary rehabilitation and non-invasive ventilation before lung surgery in very high-risk patients. Rev Mal Respir. 2013;30:414–9.

4 Respiratory Accessory Muscle, Function of Inspiratory, Expiratory, and Bulbar Muscles

Cigdem Akyol Beyoglu

Abstract

During a heavy exercise, energy requirement increases, causing insufficiency of inspiratory muscles to overcome the elastic recoil of the lungs. Respiratory accessory muscles are in charge during forced inspiration or expiration. Muscles elevating chest cage during respiration are referred to *muscles of inspiration*, while muscles depressing chest cage are termed as *muscles of expiration*. In case of high cervical spinal injury, sternocleidomastoid muscle remains intact and is the objective of physiotherapy. Expiratory muscle strength is significant in patients suffering chronic obstructive pulmonary disease. Involvement of bulbar muscles in patients with neuromuscular diseases presents a deterioration of the disease.

Keywords

Respiratory accessory muscle · Inspiratory muscles · Expiratory muscles · Bulbar muscles · Chronic obstructive pulmonary disease

Abbreviations

ALS	Amyotrophic lateral sclerosis
COPD	Chronic obstructive pulmonary disease
EMT	Expiratory muscle training
NIV	Noninvasive ventilation
SPS	Serratus posterior superior

4.1 Introduction

Diaphragm is the main muscle of breathing. During a spontaneous quiet inspiration, lungs are expanded by diaphragm muscle contraction. Contraction of diaphragm provides a 1–2 cm downward movement causing an increase in volume of thoracic cavity both in vertical and horizontal plane [1].

During a spontaneous quiet breathing, contraction of the diaphragm muscle alone is sufficient for inspiration. Two additional muscle groups are involved in primary inspiratory muscles, acting an active role during inspiration:

– External intercostal muscle contraction provides an increase in radial plane in thoracic cavity. They also strengthen the muscles and tissue between ribs to prevent retraction of

C. A. Beyoglu (✉)
Department of Anesthesiology and Reanimation, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_4

thoracic wall against negative intrapleural pressure during respiration.
– Scalene muscles: Their contraction provides an upward movement of the first two ribs.

Contraction of inspiratory muscles together provides a tidal volume during inspiration. Muscles elevating chest cage during respiration are referred to *muscles of inspiration*, while muscles depressing chest cage are termed as *muscles of expiration*. Energy required for a quiet normal respiration is 3–5% of total body energy [2]. During a heavy exercise, energy requirement maybe as high as 50-fold, even much more in case of a high resistance or a low compliance of the airways. In such cases, inspiratory muscles are insufficient to overcome the elastic recoil or tissue or airway resistance of the lungs. Respiratory accessory muscles are in charge during forced inspiration or expiration.

Main inspiratory accessory muscles are; sternocleidomastoid, sternohyoid, sternothyroid, serratus anterior, pectoralis major, and serratus posterior superior [1].

Expiration is passive in the supine position, but it becomes active during exercise or in the upright position. Abdominal and internal intercostal muscles (rectus abdominis, external and internal oblique, transversus abdominis) are the primary expiratory muscles [1]. They provide a downward movement of the ribs. Forced expiration also becomes significant in patients with chronic obstructive pulmonary disease (COPD) and neurologic disorders. An effective coughing and clearance of airways from secretions is vital for these patients; hence, a strong expiratory muscle function is fateful. Exercise increases oxygen consumption of the respiratory muscles, and increased metabolic need activates both inspiratory and expiratory accessory muscles.

4.2 Discussion and Analysis of the Main Topic

4.2.1 Accessory Inspiratory Muscles

4.2.1.1 Sternocleidomastoid Muscle

Sternocleidomastoid is a superficial neck muscle and easily observed during its contraction. Bilateral contraction elevates the clavicles. Human studies report that sternocleidomastoid showed a significant activation in case of a very high inspiratory drive or when the other rib cage muscles are inactive [3].

The sternocleidomastoid is innervated by spinal accessory nerves. Innervation of sternocleidomastoid is not adversely affected in case of a cervical spinal injury contrary to diaphragm and scalene [4]. It is the objective of respiratory rehabilitation with trapezius muscle in cervical spinal cord injury [4].

The respiratory effects of muscles are clarified adopting of reciprocity theorem of Maxwell [5]. This theorem suggests that the respiratory effect of a particular muscle ($\triangle$Pao: change in airway opening pressure) is related to mass of the muscle (m), the maximal active muscle tension per unit cross-sectional area (б), and the fractional change in muscle length ($\triangle L/L$) per unit volume increase of the relaxed chest wall $(\triangle V_L)_{Rel}$ as given below:

$$\triangle Pao = m\ б[(\triangle L/(L \triangle V_L)\ ]_{Rel}$$

In other words, a muscle that shortens during passive inflation causes a fall in Pao when it contracts alone [6]. So we can say that the respiratory effect of a given muscle maybe generalized by measuring its mass and its fractional change in length during inflation. Researchers studied the respiratory effects of intercostal muscles in humans by using this theorem [3]. By this method, Legrand and collogues compared the respiratory effect of scalenus and sternocleidomastoid, they concluded that even scalene has a greater respiratory effect, under favor of the superiority of muscle mass of sternocleidomastoid provided a similar inspiratory effect in both groups [3].

Respiratory effect of sternocleidomastoid is significant when primary inspiratory muscles are weak or insufficient. Patients undergoing mechanical ventilation weaning are at risk of diaphragmatic weakness [7]. Parthasarathy and colleagues studied 19 patients undergoing mechanical ventilation weaning in which 11 patients had failure to wean [8]. By the end of the study, sternomastoid activity was noted in all failure patients [8]. In case of diaphragmatic paraly-

sis, the respiratory effect of sternocleidomastoid is similar. Its effect becomes distinct before expiratory muscles recruit the respiratory process in case of respiratory insufficiency [8].

The sternocleidomastoid and trapezii contract at the end of maximal inspiration and during maximal voluntary ventilation in patients with severe COPD [9]. Scalenes play an active role in COPD patients. The sternocleidomastoid and trapezii in humans have a very high threshold of activation [8, 9].

As a result, sternocleidomastoid has a high activation threshold that makes it significant in cases of cervical spinal cord injury and patients undergoing weaning in mechanical ventilation.

4.2.1.2 Sternohyoid-Sternothyroid

Sternohyoid and sternothyroid muscles are infrahyoid muscles and are innervated by the first, second, and third cervical nerve roots (C1–C3). These nerve roots form ansa cervicalis. The ansa cervicalis provides motor innervation to the sternohyoid muscle [4]. Their contraction depresses the hyoid bone.

The sternothyroid muscle depresses the larynx supporting normal chewing, swallowing, and speech. Nonetheless, studies in animal models also show clear respiration-related activity in the sternothyroid [4]. A previous study reported that in 17 patients with upper aero- digestive tract cancer, sternohyoid and sternothyroid muscles showed an inspiratory activation [10]. These muscles play a critical role keeping upper airway patent during forced inspiration.

4.2.1.3 Serratus Anterior

The serratus anterior muscle derives from the first eight or nine ribs connecting to the medial border of the scapula and the thoracic vertebrae. The muscle primarily protracts and stabilizes the scapula. Thoracic nerve which is a branch of the brachial plexus innervates the muscle and the motor neurons are located in cervical segments 5–7.

Serratus anterior muscle is an accessory muscle of respiration [11]. Like other accessory muscles, its effect is distinct in case of deep breathing. Serratus anterior contraction elevates the ribs and expand thorax. A previous study reported that serratus anterior contribution to deep breathing provided a 61% increase in vital capacity in all 30 healthy human subjects [11]. Serratus anterior contribution to breathing depends on the position of the muscle. For a maximum respiratory effect, the shoulder must be fixed in a neutral position [4, 11]. Hereby, serratus anterior is an accessory inspiratory muscle which is active during high respiratory drive and highly affected by posture [12].

4.2.1.4 Pectoralis Major

Lateral and medial pectoral nerves innervate the pectoralis major. Its primary function is adduction and medial rotation of the humerus. The respiratory effect of pectoralis major during high respiratory drive has not still been revealed. A previous study reported that pectoralis major generated an inspiratory effort at 80% vital capacity against an inspiratory resistive load in healthy subjects [13]. In addition, pectoralis major contributes to expiratory flow and acts as an accessory expiratory muscle in tetraplegic patients [14]. Authors studied the peak expiratory flow rate, expiratory muscle strength in 11 completely tetraplegic patients. They concluded that pectoralis major was activated as accessory expiratory muscle and played an important role in expiratory function in tetraplegic patients.

4.2.1.5 Serratus Posterior Superior

Serratus posterior superior (SPS) originates from the lower part of the spines of the seventh cervical and upper two or three thoracic vertebrae and their supraspinous ligaments. It descends laterally and ends in external surfaces of the second to fifth ribs. It elevates the superior four ribs, raises sternum and elevates the first four ribs. This increases anteroposterior diameter of thorax.

4.2.2 Expiratory Muscles

The muscles that pull the rib cage downward during expiration are the *abdominal recti* with the most powerful effect of pulling downward of the lower ribs, and other abdominal muscles compressing the abdominal contents upward against the diaphragm are the *internal intrcostals*.

Rectus abdominis, external and internal oblique, transversus abdominis are the primary expiratory muscles. Expiratory muscle contractions reduce thoracic volume and induce exhalation. Abdominal muscle contraction promotes stretching out on diaphragm muscle fibers and contributes to mechanical effect of the diaphragm [4].

The rectus abdominis depresses the ribs during active expiration. It originates from the the 5 to seventh costa and reaches to symphysis pubis. It is separated by linea alba. The segmental nerve supply of the abdominal muscles and the overlying skin is derived from T7 to L1.

COPD may cause systemic inflammation and muscle weakness by changing the composition of muscle fibers and respiratory muscle atrophy. Physiotherapy has remarkable effects on improving muscle functions. Expiratory muscle training (EMT) strengthens the muscles, decreases airway obstruction and hyperinflation in COPD patients. Coughing effectively and forced expiration increase clearance of airway secretions and so avoid respiratory infections [15]. These advantages assist life quality and decrease hospital readmissions of COPD patients. Studies comparing inspiratory muscle training and expiratory muscle strength (EMS) report that improvements in inspiratory muscle strength increased exercise performance and decreased dyspnea, while an improvement in expiratory muscle strength was correlated with a significant increase in exercise performance alone [16]. A previous study reported significant increase (21%) in the PEmax, an improvement in the expiratory muscle endurance based on the peak expiratory pressure increase, and a significant increase (19%) in the 6 min walk test [17]. EMS training maybe used to increase PEmax, to improve speech, swallow, respiration, and physical performance.

Expiratory muscle training is often suggested in combination to inspiratory muscle training to increase exercise performance in severe COPD patients [15, 16, 18].

4.2.3 Bulbar Muscles

Bulbar muscles are composed of pharyngeal, laryngeal, and oral muscles that are used for swallowing, speaking, and coughing. In patients with neuromuscular diseases, involvement of bulbar muscle dysfunction may worsen the symptoms and decrease the quality of life. Bulbar muscle dysfunction may usually accompany amyotrophic lateral sclerosis (ALS) and myasthenia gravis. Laryngeal glottic muscles are crucial for coughing. Coughing is essential for clearance of secretions from the airways which is critical to prevent infections and progressive respiratory failure due to increased work of breathing, hypoxemia, and hypercarbia [19]. Bulbar muscle dysfunction results in an increased risk of aspiration and inadequate glottic closure during coughing. Impairment of swallowing may cause insufficient nutrition.

Patients with bulbar dysfunction are not capable of clearing their saliva from the oropharynx resulting in sialorrhea. Sialorrhea impairs quality of life and causes choking. Noninvasive mechanical ventilation (NIV) is currently a recommended treatment method in neurologic disorders. NIV improves airway patency and supports respiratory muscles causing a delay in respiratory insufficiency and invasive mechanical ventilation requirement [18]. Because of the saliva in the oropharynx, patients with sialorrhea cannot tolerate NIV treatment. Bulbar dysfunction and sialorrhea may cause aspiration and aspiration pneumonia.

Some pharyngeal muscles keep upper airway patency. Genioglossus muscle tonus keeps the tongue away from the posterior wall. Tonic activity of levator palati, tensor palati, palatopharyngeus, and palatoglossus prevents the soft palate from falling back against the posterior pharynx [20].

4.3 Conclusion Discussion

Muscles elevating chest cage during respiration are called *muscles of inspiration*, while muscles depressing chest cage are termed as *muscles of expiration*. Inspiratory and expiratory muscles support inspiration and expiration during exercise or COPD or weaning. Expiratory muscle strength is significant in patients suffering COPD. Inspiratory and expiratory muscle training strengthens these muscles and supports

forced inspiration and expiration. Patients with bulbar dysfunction are not capable of clearing their saliva from the oropharynx resulting in sialorrhea. Sialorrhea causes choking. NIV is currently a recommended treatment method in neurologic disorders. NIV improves airway patency and supports respiratory muscles causing a delay in respiratory insufficiency and invasive mechanical ventilation requirement.

Key Major Recommendations

- Accessory inspiratory muscles are in charge during exercise, or high respiratory drive.
- In case of high cervical spinal injury, sternocleidomastoid muscle remains intact and is the objective of physiotherapy.
- Expiratory muscle training in addition to inspiratory muscle training supports coughing, clearance airway, and decreases pulmonary infections.
- Bulbar muscle dysfunction accompanying neuromuscular disorders worsens the symptoms, impairs the clearance of airways, and causes coughing and intolerance to NIV.

References

1. Ulubay G. Solunum kas fizyolojisi ve kas gücü ölçümü (Respiratory mass physiology and muscle power measurement). Toraks Cerrahisi Bülteni. 2017;10:37–46.
2. Hall JE. Pulmonary ventilation. In: Guyton AC, Hall JE, editors. Textbook of medical physiology. 13th ed. Philadelphia, PA: Elsevier; 2016. p. 497–507.
3. Legrand A, Schneider E, Gevenois PA, De Troyer A. Respiratory effects of the scalene and sternomastoid muscles in humans. J Appl Physiol (1985). 2003;94:1467–72.
4. Pilarski JQ, Leiter JC, Fregosi RF. Muscles of breathing: development, function, and patterns of activation. Compr Physiol. 2019;9(3):1025–80.
5. Ad T, Boriek AM. Mechanics of the respiratory muscles. Physiological Society. Compr Physiol. 2011;1:1273–300.
6. De Troyer A, Legrand A, Wilson TA. Rostrocaudal gradient of mechanical advantage in the parasternal intercostal muscles of the dog. J Physiol. 1996;495:239–46.
7. Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, Tobin MJ. Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med. 2003;167:120–7.
8. Parthasarathy S, Jubran A, Laghi F, Tobin MJ. Sternomastoıd, rıb-cage and expıratory muscle actıvıty durıng weanıng faılure. J Appl Physiol. 2007;103(1):140–7.
9. De Troyer A, Peche R, Yernault JC, Estenne M. Neck muscle activity in patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1994;150:41–7.
10. Gehrking E, Klostermann W, Wessel K, Remmert S. Electromyography of the infrahyoid muscles - part 1: normal findings. Laryngorhinootologie. 2001;80:662–5.
11. Reid DC, Bowden J, Lynne-Davies P. Role of selected muscles of respiration as influenced by posture and tidal volume. Chest. 1976;70:636–40.
12. Legrand R, Marles A, Prieur F, Lazzari S, Blondel N, Mucci P. Related trends in locomotor and respiratory muscle oxygenation during exercise. Med Sci Sports Exerc. 2007;39:91–100.
13. Cala SJ, Edyvean J, Engel LA. Chest wall and trunk muscle activity during inspiratory loading. J Appl Physiol (1985). 1992;73:2373–81.
14. Fujiwara T, Hara Y, Chino N. Expiratory function in complete tetraplegics: study of spirometry, maximal expiratory pressure, and muscle activity of pectoralis major and latissimus dorsi muscles. Am J Phys Med Rehabil. 1999;78(5):464–9.
15. Neves LF, Reis MH, Plentz RD, Matte DL, Coronel CC, Sbruzzi G. Expiratory and expiratory plus inspiratory muscle training improves respiratory muscle strength in subjects with COPD: systematic review. Respir Care. 2014;59(9):1381–8.
16. Illi SK, Held U, Frank I, Spengler CM. Effect of respiratory muscle training on exercise performance in healthy individuals: a systematic review and meta-analysis. Sports Med. 2012;42(8):707–24.
17. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Specific expiratory muscle training in COPD. Chest. 2003;124(2):468–73.
18. Laciuga H, Rosenbek JC, Davenport PW, Sapienza CM. Functional outcomes associated with expiratory muscle strength training: narrative review. J Rehabil Res Dev. 2014;51(4):535–46.
19. Benditt OJ. Respiratory care of patients with neuromuscular disease. Respir Care. 2019;64(6):679–88.
20. Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's clinical anesthesiology. 5th ed. United States; The McGraw-Hill Companies, Inc; 2013.

Evaluation of Peripheral Airways

5

Radhika Reddy

Abstract

The small airways of the lungs are an important site of involvement in asthma and chronic obstructive pulmonary disease . The techniques in pulmonary function testing to assess small airways include spirometry, plethysmography, impulse oscillometry, inert gas washout, and exhaled nitric oxide measurement. Since each test provides unique information, a combination of these investigations will likely provide the best evaluation of small airway pathology.

Keywords

$FEF_{25–75}$ · sR_{aw} · Impulse oscillometry · FE_{NO}

Abbreviations

COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CV	Closing volume
$FEF_{25–75}$	Forced expiratory flow between 25 and 75% of the forced vital capacity
FE_{NO}	Fractional excretion of nitric oxide
FEV_1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
F_{res}	Resonant frequency
FVC	Forced vital capacity
HZ	Hertz
IOS	Impulse oscillometry
MMEF	Maximum mid-expiratory flow
MRI	Magnetic resonance imaging
PET	Positron emission tomography
$R_5–R_{20}$	Difference between the high (20 Hz) and low (5 Hz) frequency signals
RV	Residual volume
S_{III}	Slope of phase III
SPECT	Single photon emission computed tomography
sR_{aw}	Specific airway resistance
SVC	Slow vital capacity
TLC	Total lung capacity

5.1 Introduction

The small airways of the respiratory tract are an important site of involvement in diseases, such as asthma and chronic obstructive pulmonary disease (COPD). The respiratory tract is divided into 23 generations of branching airways beginning at the trachea and ending in the acinar sacs [1]. The first 15 generations of airways are the conducting airways, and do not take part in gas exchange [2].

R. Reddy (✉)
Long Beach Veteran's Affairs Medical Center
Long Beach, CA, USA
e-mail: radhika.reddy@va.gov

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_5

These conducting airways constitute anatomical dead space, which is approximately 100–150 ml in normal healthy adults. Past the conducting airways are the acinar airways, which take part in gas exchange [2]. The small airways begin at approximately generation 8 of the conducting airways and include all of the acinar airways. Early involvement of the small airways, defined as airways less than 2 ml in diameter, contributes to enhanced airway hyperresponsiveness in obstructive lung diseases, such as asthma and COPD [2]. The small airways are different from large airways, as they lack cartilaginous support and mucous glands, and are lined by surfactant, which reduces surface tension and helps to prevent collapse during expiration at low lung volumes. The small airways may be prone to pathology because of their size and the unique characteristics described [2]. Previously, small airways were thought to be a "quiet zone" because of their relatively low impact on whole resistance of the respiratory system as compared to large airways [3]. However, small airways can increase airflow resistance in the lungs significantly, contributing to approximately 10–25% of the total resistance below the larynx [2]. In COPD, small airway involvement can increase the resistance in the lungs by up to 40-fold. Small airway obstruction occurs through many mechanisms including mucous impaction, smooth muscle hypertrophy, airway wall thickening, and occlusion by inflammatory infiltrates [1]. Small airway pathology can lead to decreased airflow, increased airways resistance, gas trapping, and ventilation inhomogeneity [2]. Despite the importance of the small airways to the pathophysiology of obstructive lung diseases, they are relatively difficult to study. In this chapter, methods for analyzing small airway pathology by pulmonary function testing (PFT) will be discussed.

5.2 Discussion and Analysis of the Main Topic

There are many techniques in pulmonary function testing to assess small airways obstruction, including conventional spirometry, body plethysmography, impulse oscillometry (IOS), inert gas washout, and exhaled nitric oxide measurement [2]. Each test gives slightly different information regarding small airway pathology. No single test is adequate to assess small airway pathology, as each test has its own advantages and disadvantages [2].

5.2.1 Spirometry

The diagnosis of obstructive lung disease can be made when the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) is less than 70%. In general, reduction of FEV_1 reflects airflow obstruction in the large airways. A reduced FEV_1 is not a sensitive indicator of small airways disease [2]. Examination of the expiratory flow during mid-exhalation, the forced expiratory flow between 25% and 75% of the forced vital capacity ($FEF_{25–75}$) or maximum mid-expiratory flow (MMEF), is a commonly cited measure of small airway resistance. A value of $FEF_{25–75}$ less than 65% of predicted is considered abnormal. The theory proposed by McFadden and Linden is that obstruction in the small airways leads to reduced flow at low lung volumes, while flows at high lung volumes are much less affected [4]. McFadden and Linden studied 53 non-asthmatic smokers, and found that the only abnormalities on routine PFTs were reduced MMEF and increased residual volume (RV). In their study, airway resistance, specific conductance, FEV_1, maximum expiratory flow rate, and total lung capacity (TLC) were all within normal limits. Therefore, they proposed that MMEF represented small airway obstruction, which could be an early manifestation of chronic bronchitis. The advantage of using $FEF_{25–75}$ is that it is widely available, reproducible, and can be interpreted by standardized criteria. However, there are many disadvantages to using $FEF_{25–75}$ as a measure of small airways resistance. First, $FEF_{25–75}$ is dependent on the FVC, which is effort-dependent. Therefore, significant changes in the FVC between maneuvers will affect the $FEF_{25–75}$. Because of this, if $FEF_{25–75}$ is not adjusted for lung volumes, it will not be consistently reproducible [2]. In addition, the $FEF_{25–75}$ is not sensi-

tive for small airway disease if the FEV_1/FVC ratio is normal. In an analysis of $FEF_{25–75}$, Quanjer et al. determined that in only a small subset of cases was a low $FEF_{25–75}$ associated with normal FEV_1/FVC ratio and a normal FVC. In Quanjer's study, $FEF_{25–75}$ was abnormal in only 2.75% cases in which FEV_1, FVC, and FEV_1/FVC ratio were normal [5]. Finally, $FEF_{25–75}$ does not correlate well with other markers of small airway pathology, such as air tapping or small airway inflammation on histology [2]. Therefore, although $FEF_{25–75}$ is commonly used as a measure of small airway resistance, many experts feel that the $FEF_{25–75}$ does not contribute much to clinical decision-making [5]. Other spirometric measures have been suggested as markers of small airway obstruction. These include the forced expiratory volume in 3 s to FVC ratio (FEV_3/FVC ratio), the fraction of air not expired in the first 3 s (1 – FEV_3/FVC), the change in FVC following histamine provocation, and the ratio of FVC to slow vital capacity (SVC). Interpretations of all of these measurements must take into account the effort-dependence of these parameters.

5.2.2 Body Plethysmography

Air trapping and lung hyperinflation can be sensitively measured with body plethysmography [6]. Hyperinflation, defined as abnormally elevated lung volumes, is a function of airflow limitation, lung elastic recoil, and chest wall compliance [2]. The three measures of airway resistance determined by body plethysmography are (1) Elevation in the residual volume (RV), (2) Elevation of residual volume to total lung capacity (RV/TLC) ratio, and (3) Decreased specific airways resistance (sR_{aw}). Elevation of the RV is a measure of small airways dysfunction, as this represents gas trapping. It is a sensitive measure, as RV may increase in asthma before the onset of abnormal spirometry [2]. The degree of elevation in RV correlates with small airway inflammatory changes in COPD and peripheral airway resistance in asthma [2]. Elevation of the RV/TLC ratio is another useful marker of air trapping, especially since both RV and TLC are elevated in obstructive lung diseases. Finally, plethysmographic sR_{aw} is measured during tidal breathing [6]. sR_{aw} is a product of functional residual capacity (FRC) and airways resistance (R_{aw}) and is calculated by examining the relationship of plethysmographic box pressure and flow during spontaneous breathing. During the maneuver to measure sR_{aw}, the relationship between airflow and changes in plethysmographic pressure is assessed without the need for any special breathing maneuvers against an airway occlusion [6]. The advantage of using body plethysmography to evaluate small airways is that it is widely available, reproducible, and easy to perform. Body plethysmography is also sensitive to early changes in small airways leading to air trapping. However, these measurements are not specific for small airways, since air trapping as a result of large airway pathology also leads to abnormalities in RV, RV/TLC ratio, and sR_{aw}. Similar to spirometry, measurements of airway resistance by body plethysmography are also largely effort-dependent [2]. Another disadvantage of body plethysmography to measure peripheral airway resistance is lack of standardization. Different manufacturers have unique software, which means that the relationship between plethysmographic box pressure and airflow can be analyzed in different ways, contributing to error [6]. Therefore, interpretation of these measurements must be done with caution, taking into consideration the effort-dependence of this parameter, and lack of standardization.

5.2.3 Impulse Oscillometry

Impulse oscillometry is a technique that applies oscillating pressure variations in the form of sound waves at frequencies from 5 to 35 Hertz (Hz), to assess respiratory mechanics during spontaneous breathing [7]. Pressure and flow changes are measured at the mouth and analyzed in a Fourier transformation to determine the impedance of the respiratory system [2]. Resistance measured by IOS includes resistance of the oropharynx, larynx, trachea, large and small airways, and lung and chest wall [7].

Higher frequencies (>15 Hz) reflect a contribution of the large airways, as these signals are absorbed before they reach the small airways. Low frequencies (5 Hz) represent the whole lung since they penetrate deep into the lung. Therefore, the contribution of the peripheral airways is determined by examining the difference between the high- and low-frequency signals (R_5–R_{20}) [2]. Currently, R_5–R_{20} is the only IOS parameter used for the diagnosis of small airway dysfunction. The documented value for small airway dysfunction in COPD patients and those exposed to dust/fumes is R_5–R_{20} greater than 0.07 kPa/(L/s) [6]. Another possibly important IOS parameter aside from R_5–R_{20} is resonant frequency (F_{res}), which represents the frequency at which reactance is 0, indicating that elastic and inert properties are equal and opposite. The normal F_{res} is between 6–11 Hz [7]. In a study by Chiu et al., the IOS parameter F_{res} as compared to R_5–R_{20} and $FEF_{25–75}$ had increased sensitivity in detecting small airway dysfunction in patients without obstructive lung disease [8]. The main advantage of IOS is that it is effort-independent, unlike spirometry and body plethysmography, and therefore is consistently reproducible [7]. Since IOS does not rely on forced maneuvers, it can be performed easily on patients with severe lung disease and patients who cannot reliably perform spirometry [2]. Additionally, IOS is more sensitive in detecting small airway dysfunction than spirometry and body plethysmography [8]. Other advantages of IOS are its noninvasiveness, relative ease to perform, and ability to provide intra-breath analysis. The main disadvantage of IOS is that it is a relatively newer test, and therefore equipment may not be widely available. Since it provides intra-breath analysis, there may be significant moment-to-moment variability in a stable individual [7]. Therefore, multiple measurements may be required to obtain a reliable true value in an individual. In addition, there may be some interference from swallowing and upper airway artifacts in the interpretation of IOS [2]. Overall, some experts feel that IOS may be the best individual test to actually measure small airway dysfunction.

5.2.4 Inert Gas Washout

Inert gas washouts, which measure efficiency of gas mixing in the lungs, are another way of evaluating the peripheral airways. Overall, they assess the efficiency of the distribution of ventilation. Washout tests can provide important insight into mechanisms behind abnormal ventilation distribution and help localize airway pathology [9]. The most common techniques used are the single breath nitrogen washout (SBNW) and the multiple breath nitrogen washout (MBNW) [2]. The SBNW is performed by inhaling 100% oxygen from RV to TLC, followed by a slow exhalation maneuver. Subsequently, the exhaled volume and concentration of nitrogen are measured, which can be broken down into four phases [2]. Phase I represents anatomical dead space, the air in the conducting airways of the lungs, and the concentration of nitrogen is close to 0%. Phase II is characterized by a sharp rise in nitrogen concentration as the alveolar gas mixes with dead space gas. During Phase III, the concentration of nitrogen plateaus, as this represents alveolar gas. Phase IV is characterized by a steep rise in nitrogen concentration as the most poorly ventilated areas of the lung empty [2]. Analysis of the slope of Phase III (S_{III}) can give important information regarding small airway pathology. In obstructive lung disease, the affected lung units mix less well with inspired oxygen and empty more slowly, leading to an increase in S_{III}. Another important measurement in obstructive lung disease is the closing volume (CV), which is the point where small airways start to close due to gravity-dependent closing. CV represents airway closure occurring preferentially in dependent lung regions and peripheral airway obstruction [9]. The advantage of SBNW is that it is sensitive to early changes in patients with obstructive lung disease. Asthmatic patients with normal FEV_1 have increased CV and S_{III} compared to healthy controls, which indicates that measures may be more sensitive than spirometry [2]. However, SBNW is not very specific, as changes in both large and small airways can affect the S_{III}. Therefore, it is possible to infer that a normal S_{III} indicates no small airway pathology, but an

abnormal S_{III} does not help differentiate between small and large airway pathology. In addition, SBNW is not widely used as it requires special equipment, often restricting it to research settings [2]. During a MBNW test, the patient inhales 100% oxygen from FRC with a fixed tidal volume and respiratory rate. The test stops when the exhaled nitrogen is less than 1/40th of the original concentration. Similar to SBNW, the S_{III} is measured over multiple breaths. Advantages and disadvantages are similar to SBNW [2]. Other inert gases, such as helium and sulfur hexafluoride can be used in washout tests as well, and may offer further information from the S_{III} measurement. However, these inert gases are not as readily available, require a wash-in period, and special equipment to perform the test. Nitrogen washout has the advantage of being widely available and affordable. In addition, nitrogen is resident in the lungs, even in slowly ventilated lung compartments, and therefore is more sensitive in detecting abnormalities as compared to the other inert gases [9].

5.2.5 Exhaled Nitric Oxide

Measurement of the fractional excretion of nitric oxide (FE_{NO}) is another way to examine peripheral airways disease. Nitric oxide is formed by nitric oxide synthase-mediated cleavage of a guanido group of arginine to form citrulline and nitric oxide [9]. FE_{NO} is measured by single breath exhalation during tidal breathing [2]. FE_{NO} is often up to fivefold higher in asthmatic patients as compared to normal control patients [10]. The FE_{NO} value reflects levels of inflammation in the lungs since alveolar and inflammatory cells produce nitric oxide [2]. Many studies have shown that levels of FE_{NO} correlate with levels of eosinophilic airway inflammation seen in bronchoalveolar lavage (BAL) fluid, induced sputum, and endobronchial biopsies [10]. In addition, FE_{NO} levels increase during asthma exacerbations or periods of increased symptoms, and may actually predict exacerbations in some patients [9]. Exhaled nitric oxide is dependent on flow rate, which can help localize areas of inflammation within the lung. Under low flow, FE_{NO} reflects central airways, and under high flow, it represents the alveolar nitric oxide [2]. FE_{NO} has been commonly used for the evaluation of patients with asthma. In a study by Spergel et al., FE_{NO} correlated more closely with asthma symptoms than did FEV_1, indicating that it is a good indicator of asthma control [10]. A FE_{NO} greater than 25 in asthmatic patients indicates significant eosinophilic inflammation, which improves with treatment with both oral and inhaled corticosteroids. In COPD, FE_{NO} may be raised, but usually to a lesser extent than in patients with asthma. The advantage of FE_{NO} is that it is easy to perform and sensitive to treatment in asthma patients. However, its disadvantages are its unclear role in COPD, and the fact that it is affected by smoking status, which may affect the interpretation [2].

5.3 Conclusion Discussion

In conclusion, understanding small airway pathology in asthma and COPD is important, as it may distinguish individual phenotypes of the diseases and guide therapies. There are many techniques in pulmonary function testing to assess small airways obstruction, including conventional spirometry, body plethysmography, impulse oscillometry, inert gas washout, and exhaled nitric oxide measurement. Spirometry and plethysmography are easy to perform, however are effort-dependent and are not specific for small airway pathology. FE_{NO} is easy to perform and well-studied in asthma, however has an unclear role in COPD. Inert gas washouts and IOS are sensitive to early changes in small airway pathology, but require special equipment to perform. Aside from pulmonary function testing, imaging of the lungs by computed tomography (CT) scans can be used to assess small airway pathology. Assessing CT images for mosaic attenuation, areas of low attenuation, can further localize areas of air trapping within the small airways. In addition, sputum analysis, transbronchial biopsy, and bronchoalveolar lavage can also provide additional information regarding small airway pathology [2]. In the near future, mag-

netic resonance imaging (MRI) and nuclear medicine tests including two-dimensional gamma scintigraphy, single photon emission computed tomography (SPECT), and positron emission tomography (PET) may have emerging roles in evaluating the small airways [1]. Currently, many of these specialized tests require special equipment, and are therefore restricted to the realm of research. Hopefully in the future, more research can be done to incorporate these tests and further our understanding of small airway pathology. Overall, since each test provides unique anatomical, functional, and physiological information, a combination of these investigations will likely provide the best evaluation of small airway pathology.

Key Major Recommendations

- Examination of the $FEF_{25–75}$ (or MMEF) is a commonly cited measure of small airway resistance. This spirometric measurement is widely available and reproducible, however is effort-dependent, not specific for small airways disease, and may not be very clinically significant.
- The three measures of airway resistance determined by body plethysmography are (1) Elevated RV. (2) Elevated RV/TLC ratio. (3) Decreased sR_{aw}. These measurements are easy to perform and sensitive to early changes in small airways, but are effort-dependent and not specific for small airways disease.
- IOS is a technique that applies oscillating pressure variations to assess respiratory mechanics during spontaneous breathing. IOS is more sensitive in detecting small airway dysfunction than spirometry and body plethysmography, and is effort-independent, which is an advantage. Some experts feel that IOS may be the best individual test to actually measure small airway dysfunction.
- Inert gas washouts are sensitive to early changes in obstructive lung disease and can distinguish small airway pathology. However, these tests often require special equipment, therefore restricting them to research settings.
- FE_{NO} can help evaluate inflammation in the lungs, is easy to perform, and is sensitive to treatment changes in asthmatic patients, however, its role in COPD is unclear.

References

1. Desh D, Prasad A, Atwal SA, Agarwal K. Recognition of small airways dysfunction in asthma and COPD – the road less travelled. J Clin Diagn Res. 2017;11(3):TE01–5.
2. McNulty W, Usmani O. Techniques of assessing small airways dysfunction. Eur Clin Respir J. 2014;17:1.
3. Mead J. The lung's "quiet zone". N Engl J Med. 1970;282:1318–9. https://doi.org/10.1056/NEJM197006042822311.
4. McFadden ER Jr, Linden DA. A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small-airways disease. Am J Med. 1972;52:725–37.
5. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, et al. Measurement of $FEF_{25–75\%}$ and $FEF_{75\%}$ does not contribute to clinical decision-making. Eur Respir J. 2014 Apr;43(4):1051–8.
6. Kirkby J. Plethysmographic assessment of airway resistance. https://www.ers-education.org/lrmedia/2016/pdf/298399.pdf.
7. Goldman MD, Saadeh C, Ross D. Clinical applications of forced oscillation to assess peripheral airway function. Respir Physiol Neurobiol. 2005;148:179–94.
8. Chiu HY, Hsiao YH, Su KC, Lee YC, et al. Small airway dysfunction by impulse oscillometry in symptomatic patients with preserved pulmonary function. J Allergy Clin Immunol Pract. 2020;8(1):229–235.e3. https://doi.org/10.1016/j.jaip.2019.06.035.
9. Robinson PD, Latzin P, Verbanck S, Hall GL, et al. Consensus statement for inert gas washout measurement using multiple- and single-breath tests. Eur Respir J. 2013;41:507–22. https://doi.org/10.1183/09031936.00069712.
10. Spergel JM, Fogg MI, Bokszczanin-Knosala A. Correlation of exhaled nitric oxide, spirometry and asthma symptoms. J Asthma. 2005;42(10):879–83. https://doi.org/10.1080/02770900500371344.

Lung Compliance Measurement

6

Mohamad F. El-Khatib

Abstract

Measurements of respiratory mechanics and particularly the lung compliance are done widely in patients receiving mechanical ventilation. This can provide information about the severity of disease, the response to treatment, and the safety for ventilator discontinuation. Measuring lung compliance and making appropriate ventilator adjustments can lead to improved outcomes in patients receiving mechanical ventilation. The focus of this chapter is on the measurement of lung compliance and how this can be used to help make clinical decisions.

Keywords

Lung compliance · Static · Dynamic
Noninvasive ventilation · Mechanical ventilation

Abbreviations

ARDS	Acute respiratory distress syndrome
BiPAP	Bilevel positive airway pressure
C_{CW}	Chest wall compliance
C_{dyn}	Dynamic compliance
C_L	Lung compliance
C_{RS}	Respiratory system compliance
C_{stat}	Static compliance
ECMO	Extracorporeal membrane oxygenation
EPAP	Expiratory positive airway pressure
IPAP	Inspiratory positive airway pressure
PEEP	Positive end expiratory pressure
PIP	Positive inspiratory pressure
P_{peak}	Peak airway pressure
$P_{plateau}$	Plateau pressure
V_T	Tidal volume
V_{TE}	Expired tidal volume
V_{TI}	Inspired tidal volume
ΔP	Change in pressure
ΔV	Change in volume

6.1 Introduction

Measurements of respiratory mechanics allow a clinician to monitor closely the course of pulmonary disease. At the bedside, changes in these mechanics can occur brusquely or they may reveal slow trends in respiratory condition. Due to its strong correlation with the underlying pathophys-

M. F. El-Khatib (✉)
Department of Anesthesiology, Division of Respiratory Therapy, American University of Beirut—Medical Center, Beirut, Lebanon
e-mail: mk05@aub.edu.lb

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_6

iology in lung diseases, the measurement of lung compliance (C_L) is highly desired whether the patient is receiving invasive or noninvasive mechanical ventilation or just spontaneously breathing. In acute hypoxemic respiratory failure such as acute respiratory distress syndrome (ARDS), the decrease in lung compliance is attributable to the impairment of surfactant function, alveolar fluid accumulation, and reduction of airspace volume due to alveoli collapse [1]. Most of the lung diseases are nonhomogeneous with areas of lung consolidation and atelectasis along with nearly normally aerated lung portions with nearly normal intrinsic mechanical properties [1]. From this perspective, diseased lung is stiffer with decreased compliance simply because of reduced aeration of some of its portion.

The assessment of C_L helps in titrating and optimizing ventilatory support as well as for monitoring the progression of the lung disease. In most modalities of invasive and noninvasive ventilatory support, it is the respiratory system compliance (C_{RS}) rather than the lung compliance (C_L) that is directly determined. C_{RS} not only reflects C_L but also reflects the chest wall compliance (C_{CW}) that are two separate compliances interacting in parallel to make the respiratory system compliance [2]. To separate between the lung and chest wall compliances, an esophageal catheter incorporating a balloon needs to be inserted into the patient's esophagus for estimation of the pleural pressure and appropriate separate estimation of C_L and C_{CW} [2]. Although C_{RS} is affected by both C_L and C_{CW} (Table 6.1), the changes in C_{RS} most commonly result from changes in C_L rather than C_{CW} since the C_{CW} does not change significantly during the course of the lung diseases and as such in most of the cases, the C_{RS} is considered an acceptable surrogate of the C_L. For the purpose of this chapter, it will be assumed that C_{CW} is stable and measurement of C_{RS} will serve as an accurate reflection of C_L.

Table 6.1 Causes for decreases in respiratory system compliance

Decrease in lung compliance	Decrease in chest wall compliance
Tension pneumothorax	Obesity
Mainstem intubation	Ascites
Dynamic hyperinflation	Neuromuscular weakness
Pulmonary edema	Flail chest
Pulmonary fibrosis	Kyphoscoliosis
Acute respiratory distress syndrome	Fibrothorax
Hypersensitivity pneumonitis	Chest wall tumor
Connective tissue disorders	Paralysis
Sarcoidosis	Scleroderma
Lymphangitic spread of tumor	

6.2 Discussion and Analysis of the Main Topic

6.2.1 Techniques for Measurement of Lung Compliance

In an expandable structure such as the lung, the compliance is the most important mechanical property that reflects the ability of the lung to stretch and absorb the applied pressures and delivered tidal volumes. The compliance is directly proportional to the change in volumes (ΔV) but indirectly proportional to the change in pressures (ΔP) and is expressed as the ratio $\Delta V/\Delta P$. The change in volume is simply the tidal volume ($\Delta V = V_T$) while the change in pressures is the change from peak pressure at the end of inspiration (PIP) to the total positive end expiratory pressure ($PEEP_{Tot}$) ($\Delta P = PIP - PEEP_{Tot}$). Whenever there is no auto-PEEP, the $PEEP_{Tot}$ is simply the applied PEEP and subsequently the lung compliance is expressed as $C_{RS} = V_T/(PIP - PEEP)$.

6.2.1.1 Measurement of Lung Compliance During Invasive Mechanical Ventilation

In mechanically ventilated patients, two types of lung compliances can be determined: static (C_{stat}) and dynamic (C_{dyn}) lung compliances. All current generations of mechanical ventilators provide comprehensive monitoring of key variables, such as inspired and expired tidal volumes (V_{TI} and V_{TE}), peak airway pressure (P_{peak}), PEEP and auto-PEEP that are useful for the determination of both static and dynamic lung compliances. During mechanical ventilation, the static lung compliance is usually a better reflection of the lung parenchyma and alveoli since it is deter-

mined during a static steady-state during periods of no gas flows that will eliminate any possible effects of the airways' resistance. Periods of no flows are created by clinicians at the bedside where end-inspiratory pauses/holds of variable lengths are created. This is referred to as an "end-inspiratory hold maneuver" during which the peak alveolar pressure or plateau pressure ($P_{Plateau}$) rather than the peak airway pressure is determined that specifically reflects the ability of alveoli and the lung as a whole to stretch and absorb the delivered tidal volume (Fig. 6.1). Knowing the $P_{Plateau}$, the static C_L will be V_T/($P_{Plateau}$ − PEEP). The most accurate approximation of $P_{Plateau}$ is obtained when patients are passive and when adequate end-inspiratory holds (≥0.5 s) are applied.

On the other hand, dynamic lung compliance represents lung compliance during periods of gas flow where the airway resistance can influence the generated peak inspiratory pressure. Dynamic lung compliance is calculated as V_T/(PIP − PEEP) (Fig. 6.1). Dynamic lung compliance is always lower than or equal to static lung compliance, because (PIP − PEEP) is always greater than ($P_{Plateau}$ − PEEP). For example, in a mechanically ventilated patient with V_T of 450 mL, PEEP of 8 cmH_2O, PIP of 35 cmH_2O, auto-PEEP of 0 cmH_2O, and $P_{plateau}$ of 24 cmH_2O, then the C_{stat} = 450/(24–8) = 28.125 mL/cmH_2O and C_{dyn} = 450/(28–8) = 22.5 mL/cmH_2O. In a normal subject on mechanical ventilation, static compliance should be greater than 40–50 mL/cmH_2O while dynamic compliance should be greater than 30 mL/cmH_2O [3].

6.2.1.2 Lung Compliance Measurement During Noninvasive Mechanical Ventilation

Assessment of lung compliance is particularly difficult during noninvasive ventilation due to the fact that the patient is not passive, and it is almost impossible to measure the contribution of patient respiratory muscles to the total driving pressure. However, during noninvasive ventilation such as bilevel positive airway pressure (BiPAP), dynamic lung compliance can be estimated because during BiPAP support, it is almost impossible to create periods of no gas flow at the end of inspiration as well as to achieve stable plateau pressures that are necessary for the determination of static lung compliance. Periods of no gas flow at the end of inspiration are best created and maintained when patients are passive which is not the case during BiPAP therapy. Nevertheless with modern BiPAP devices, the tidal volumes are accurately determined particularly if unintended leaks (e.g., leaks around the patient's interface) are minimized/eliminated which allows the clinicians to appropriately estimate the dynamic lung compliance as V_T/(IPAP – EPAP), where IPAP is the inspiratory positive airway pressure and EPAP is the expired positive airway pressure. For example, in a patient receiving noninvasive ventilation with

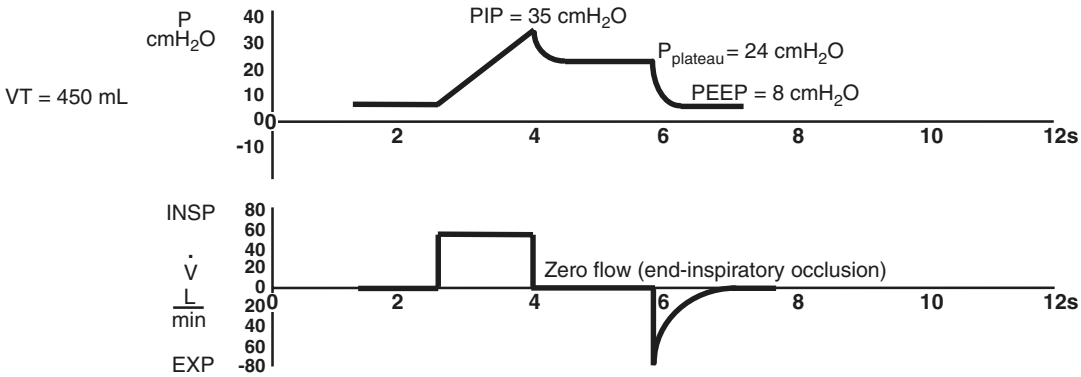

Fig. 6.1 Determination of lung compliance during mechanical ventilation

BiPAP, if the IPAP is 14 cmH_2O, EPAP is 8 cmH_2O, and exhaled tidal volume is 300 mL, then C_{dyn} = 300/(14–8) = 50 mL/cmH_2O.

The obvious advantage for dynamic compliance is that it is continuous, and can be used as ventilator treatment is applied. Dynamic compliance is more for monitoring than for measurement, and its lack of precision is counterbalanced to some degree by its capacity to follow trends and changes in lung mechanical properties.

6.2.1.3 Lung Compliance Measurement in Spontaneously Breathing Patients

Modern and comprehensive systems for pulmonary function testing that include a body plethysmograph (body box) have the capability for measurement of respiratory system compliance in spontaneously breathing patients. The body plethysmography is a very sensitive lung measurement used to detect complex or mixed lung pathology. Body plethysmography involves the patient breathing against a shutter valve while sitting in a body box. The pressure changes in the box helps measure the lung volumes [4]. Once different readings of the lung volume are obtained at specific measured pressure points, a pressure–volume curve representing both elastic and airway resistance of the lung is obtained and subsequently the dynamic compliance of the lung is determined as the resulting slope of pressure–volume curve (i.e., $C_{dyn} = \Delta P/\Delta V$) [4].

6.2.1.4 Factors Affecting Pulmonary Compliance

There are several factors that can affect the lung compliance. These include elastic property of the lung tissue, the surface tension elastic force, surfactant, and age.

Elastic property of the lung tissue is determined by the collagen and elastin fibers inside the lung parenchyma. The flexibility of these fibers determines the compliance of the lung. These fibers could be damaged or affected by some pulmonary pathologies and cause the lung to be stiff with low compliance [1].

The surface tension exerted by the fluid lining the walls of the alveoli is another factor that affect the lung compliance [1]. Thus, the saline-filled lung has higher compliance than the normal air-filled lung.

Surfactant is the surface-active agent in the fluid, secreted by type II alveolar epithelial cells lining the alveoli. It reduces the surface tension in the alveoli and indirectly affects the compliance of the lung. In lung pathologies where surfactant production is compromised, the lungs are usually collapsed and hard to inflate due to the low compliance [1].

Finally, age can minimally influence the lung compliance. The small increases in lung compliance with age are mainly due to the extent of structural changes in the lung elastin fibers [5].

6.3 Conclusion Discussion

6.3.1 Discussion

Lung compliance represents the major load on the respiratory muscles and can be responsible for up to 60% of the work of breathing. For lungs with low compliances, more work from breathing muscles is required to inflate the lungs. Xie et al. showed that the respiratory system compliance affected the relationships between tidal volume and driving pressure and lung strain in ARDS patients. These results indicate that increasing tidal volume-induced lung injury more easily in patients with low respiratory system compliance [6].

In specific pathologies, continuous monitoring of the lung compliance curve is useful to understand the progression of the condition and to decide on therapeutic settings needed for ventilator management [7]. In 154 ARDS patients, Bellani et al. showed that lower respiratory system compliance (odds ratio, 0.92 [0.88–0.96]) are independently associated with increased mortality [8]. Moreover, they also showed that the respiratory system compliance significantly correlated with the volume of aerated lung

($r = 0.69$). Furthermore, in 787 ARDS patients, Guerin et al. showed that when lung protective mechanical ventilation is applied, the respiratory system compliance was a risk factor for mortality [9]. In an international, multicenter, prospective cohort study of 350 patients undergoing extracorporeal membrane oxygenation (ECMO) for ARDS during a 1-year period in 23 international ICUs, Schmidt et al. showed that improvements in C_{stat} post-ECMO were associated with better outcomes [10].

The lung compliance has been used to guide for the optimal level of PEEP in patients with acute respiratory distress syndrome (ARDS). Different values of static compliances are determined by applying different levels of PEEP in intubated and mechanically ventilated ARDS patients, and the PEEP resulting in the highest value for static compliance is selected and considered as the "PEEP of best compliance." Usually, this will correspond to the least ventilation to perfusion mismatch, lowest dead-space fraction, and the maximum oxygen delivery. When compared to FiO_2-driven positive end expiratory pressure in 159 patients with severe ARDS, Pintado et al. showed that individualized PEEP selection based on the best static compliance was associated with lower mortality at 90 days, with an increase in organ dysfunction-free days at 28 and 90 days [11].

Also, several reports have indicated that improvements in lung compliance back to normal values are good indicators for weaning ventilatory support and liberation from mechanical ventilation [3, 12].

6.3.2 Conclusion

Monitoring of respiratory mechanics and particularly lung compliance is of utmost importance in patients receiving invasive or noninvasive ventilatory support. Bedside measurements of lung compliance can be used for the diagnosis of various illnesses and to assist in the proper ventilatory support management to optimize outcomes. In mechanically ventilated patients, measurements of lung compliance can provide information about the severity of disease, the response to treatment, and the safety of ventilator discontinuation. Most modern ventilators incorporate technologies and algorithms that allow continuous measurements of lung compliance that is most accurate when patients are passive and receiving controlled mechanical ventilation. The patients on noninvasive ventilatory support still present a challenge and new technologies and algorithms for monitoring of lung compliance need to be developed to facilitate management and improve outcomes in those patients.

Key Major Recommendations

- Monitoring of lung compliance is vital for the management of invasive and noninvasive mechanical ventilation.
- In mechanically ventilated patients, measurements of lung compliance can provide information about the severity of disease, the response to treatment, and the safety of ventilator discontinuation.
- Making appropriate ventilatory support adjustments based on lung compliance can lead to improved outcomes in selected patients.

References

1. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA. 2018;319(7):698–710.
2. Hess DR. Respiratory mechanics in mechanically ventilated patients. Respir Care. 2014;59(11):1773–94.
3. MacIntyre NR. Evidence-based guidelines for weaning and discontinuing ventilatory support. Chest. 2001;120:375S–96S.
4. Kraman S. Lesser used tests of pulmonary function: compliance, resistance and dead space. COPD. 2007;4(1):49–54.
5. Lalley PM. The aging respiratory system—pulmonary structure, function and neural control. Respir Physiol Neurobiol. 2013;187(3):199–210.
6. Xie J, Jin F, Pan C, et al. The effects of low tidal ventilation on lung strain correlate with respiratory system compliance. Crit Care. 2017;21(1):23–31.

7. Lu Q, Rouby JJ. Measurement of pressure-volume curves in patients on mechanical ventilation: methods and significance. Crit Care. 2000;4(2):91–100.
8. Bellani G, Grassi A, Sosio S, et al. Driving pressure is associated with outcome during assisted ventilation in acute respiratory distress syndrome. Anesthesiology. 2019;131(3):594–604.
9. Guérin C, Papazian L, Reignier J, et al. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care. 2016;20:384–93.
10. Schmidt M, Pham T, Arcadipane A, et al. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome. An International Multicenter Prospective Cohort. Am J Respir Crit Care Med. 2019;200(8):1002–12.
11. Pintado M-C, de Pablo R, Trascasa M, et al. Compliance-guided versus FiO2-driven positive-end expiratory pressure in patients with moderate or severe acute respiratory distress syndrome according to the Berlin definition. Med Intensiva. 2017;41(5):277–84.
12. El-Khatib M, Bou-Khalil P. Clinical review: liberation from mechanical ventilation. Crit Care. 2008;12(4):221–33.

7 Evaluation of Pressure, Volume, and Flow Waveforms During NIV

Sara Dias, Antonio M. Esquinas, Bruno Cabrita, and Ana Luísa Fernandes

Abstract

Noninvasive ventilation (NIV) has become the standard of care for the management of acute or chronic respiratory failure in many situations. However, to successfully ventilate a patient, leaks and patient-ventilator synchrony should be optimized. Monitoring pressure, volume, and flow waveforms displayed by the ventilators may help to improve patient-ventilator interaction and, therefore, lead to effective ventilation.

Keywords

Noninvasive ventilation · Waveforms · Monitoring · Asynchrony

Abbreviations

ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
I/R	Inspiration/expiration ratio
NIV	Noninvasive ventilation
Paw	Airway pressure
PEEPi	Intrinsic positive end-expiratory pressure
VTE	Expiratory vital volume

S. Dias (✉) · B. Cabrita · A. L. Fernandes
Pulmonology Department, Hospital Pedro Hispano, Matosinhos, Portugal

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

7.1 Introduction

NIV is a life-saving therapeutic option that should be proposed to the majority of patients with acute respiratory failure (ARF) when mechanical ventilation is not indicated. However, the benefits of NIV can only be obtained if adequate monitoring of patients is undertaken [1]. Monitoring flow, pressure, and volume curves, at least in the beginning of ventilation, is one of the keys to success. The analysis of these signals in real-time is particularly useful for evaluating the interaction between the patient and the machine.

7.2 Discussion and Analysis of the Main Topic

7.2.1 Monitoring Pressure, Volume, and Flow Waveforms as a Key to Success

Since NIV is a semi-open system, there are inevitable leaks associated: nonintentional leaks (through the mouth, when using a nasal mask, or around the interface) and intentional leaks

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_7

(through expiratory ports or valves, which are part of the circuit). Ideally, the ventilator should identify leaks and automatically adjust triggering and cycling-off functions to compensate them. Compensation of leakage is usually performed by most ventilators unless there are excessive leaks, which have a negative effect on the effectiveness of NIV. This is related to changes in the actual tidal volume that the patient receives and impaired triggering and cycling-off functions of the ventilator [2].

Asynchrony is defined as the uncoupling of ventilator-delivered inspiratory flow from the patient's ventilatory demands, in terms of either timing or drive [3]. Several variables interfere with the incidence and severity of asynchrony: ventilation mode, ventilator settings, respiratory system mechanics, presence of air leaks, and the type of interface. The prevalence of various asynchrony events in a group of 60 patients receiving NIV for ARF was between 12% and 23% and severe asynchrony was observed in 43% of the patients. The most frequent asynchrony was delayed cycling, which was present in 23% of the patients. This was followed by double triggering (15%), auto-triggering (13%), ineffective efforts (13%), and premature cycling (12%) [4].

The flow, volume, and airway pressure (Paw) signals displayed in the monitor of new-generation ventilators are of great help in the identification of several aspects of patient-ventilator interaction. A careful inspection of these signals may help the caregiver to recognize triggering delay, ineffective efforts, and auto-triggering and to estimate the patient's respiratory efforts [5].

In a review made by *Ergan* et al., the authors suggest the use of devices with flow and pressure waveforms in real-time and support with ventilation parameters as numerical data: leaks, inspiratory and expiratory tidal volumes, minute ventilation, inspiratory time, respiratory rate, and inspiration/expiration (I/E) ratio [1]. Despite the evaluation of patient-ventilator asynchrony, waveform analysis during NIV may also inform about the quality of ventilation, which is related to the magnitude of leaks, obstruction of airways, and the I:E ratio. In a study conducted by *Di Marco* et al. on a cohort of patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), it was shown that the titration of ventilator settings based on the analysis of respiratory waveforms in real-time resulted in a more rapid improvement in pH and arterial pressure of carbon dioxide and a better tolerance of ventilation by patients. Moreover, the analysis of flow and pressure waveforms on the screen induced physicians to use higher levels of external positive end-expiratory pressure (PEEP), more sensitive inspiratory triggers, and a faster speed of pressurization. [6]

7.2.2 Monitoring Basic Parameters

Expiratory vital volume (VTE) is an essential parameter to monitor, as it reflects alveolar ventilation. It is either measured directly by a proximal flow sensor in a double-limb circuit system or calculated from the integral of the flow signal with adjustments for unintentional leaks in a single-limb circuit system. For example, when using pressure-support ventilation mode, for a certain level of inspiratory pressure provided the obtained tidal volume may vary. This variation is the result of several physiological variables: resistance of airways, compliance of the lungs and chest, the patient's respiratory effort, and time of inspiration. [1] Before starting NIV, the desirable VTE should be calculated based on the ideal body weight and ranges from 6 ml/kg for neuromuscular and restrictive chest wall disorders to 8–10 ml/kg in obstructive diseases and obesity. [7]

However, parameters displayed by the ventilator may have limited accuracy, as is the case of ineffective efforts, in which the ventilator respiratory rate will be lower than the patient's respiratory rate. It has been proved that VTE reported by ventilator software may differ significantly from the real values. [1]

Unlike invasive ventilation, NIV is a nonhermetic system, which allows a certain level of leaks, and it has to overcome a variable resistance inherent to the upper airway. These features associated with NIV may compromise the delivery of

an effective tidal volume, not necessarily affected by increasing the delivered volume or the delivered inspiratory pressure. Also, these features will influence monitorization through flow or pressure waveforms. [8]

Intermittent obstruction of the upper airway commonly happens during NIV and it can be related to obstructive events at the oropharynx, as a result of insufficient expiratory airway pressure and unstable upper airway, or to episodes of intermittent obstruction related to cyclic glottic closure induced by hyperventilation. [8]

The relation between inspiratory and expiratory times, or the I:E ratio, is indirectly determined by other parameters, as respiratory rate and inspiratory flow, and it reflects the efficiency of lung's deflation and the risk of hyperinflation. In obstructive disorders, the I:E ratio should be 1:3 or greater to minimize dynamic hyperinflation, by enabling a longer expiratory time. On the other hand, the I:E ratio should be around 1:1 when we are dealing with restrictive disorders, such as neuromuscular or chest wall diseases. [7]

7.2.3 The Relevance of Intrinsic Positive End-Expiratory Pressure

Obstructive airway diseases are usually associated with the presence of intrinsic positive end-expiratory pressure (PEEPi), which is related to dynamic hyperinflation, which means that end-expiratory lung volumes are exceeding functional residual capacity. [1] Patients with severe COPD generate suboptimal inspiratory and transdiaphragmatic pressures, explained by hyperinflation-induced diaphragm shortening, restraining its ideal movement range. [5] This, combined with airflow limitation caused by narrowed airways, leads to positive alveolar pressure at the end of the expiration. Inevitably, inspiratory muscles require extra effort to reduce alveolar pressure to a subatmospheric level for the next breath, thus resulting in increased workload. [7, 8]

PEEPi has a negative impact on ventilator triggering because inspiratory flow only starts after PEEPi is counterbalanced. Indeed, a portion of the pressure exerted by respiratory muscles is dissipated to overcome PEEPi, which leads to a delay between the beginning of inspiratory effort and the triggering. In some cases, the inspiratory effort of the patient is not able to counterbalance PEEPi, resulting in an inability to trigger the ventilator-ineffective efforts. [5] So, PEEPi assessment and the application of an external PEEP by the ventilator may reduce work of breathing, improve patient-ventilator synchrony, and increase VTE. [1] In some ventilators, it is called the expiratory positive airway pressure. Providing an external PEEP during NIV has many other advantages: flushing CO_2 from the dead space, preventing rebreathing within the mask, preserving the airway patency in patients with unstable upper airway during sleep, and recruiting alveoli. [8]

However, setting the PEEP level beyond PEEPi may be harmful, so it is recommended to set PEEP at 50–80% of PEEPi. [7]

The degree of PEEPi can be measured invasively with an esophageal pressure transducer. It corresponds to the negative deflection of esophageal pressure from the onset of inspiratory effort to the point of zero flow at end-expiration (see Fig. 7.1). [1] This is not performed routinely, as it requires special equipment and experienced staff. When referring to NIV, the presence and the degree of PEEPi can be identified by inspection of the expiratory flow-time curve. [1]

7.2.4 Evaluation of Leaks

As mentioned before, excessive leaks have a detrimental effect on the efficiency of NIV, and for that reason, all types of air leaks should be monitored. Large air leaks interfere with the effectiveness of the treatment, as they may cause a significant drop in the delivered intra-alveolar pressure, reduce the tidal volume, and lead to patient-ventilator asynchrony by affecting trigger functions. On the other hand, small air leaks can disturb the patient, cause conjunctivitis, or create noise. [9]

Inspection of the pressure, volume, and flow waveforms provided by the new-generation ven-

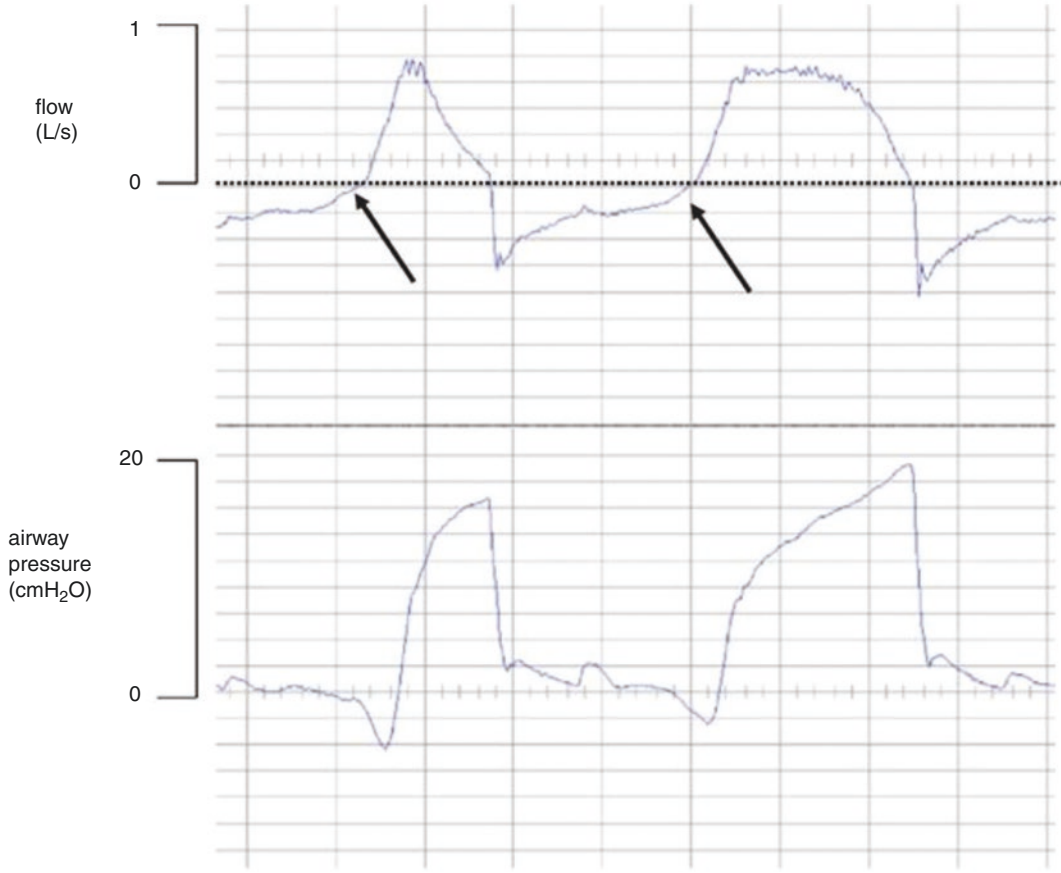

Fig. 7.1 Waveforms suggestive of the presence of intrinsic positive end-expiratory pressure (PEEPi): expiratory flow curve does not reach the zero-flow line when the inspiration starts (arrows), suggesting that the expiratory time was not sufficient for lung emptying. Reprinted with permission from Springer: Nava and Fanfulla F, Non Invasive Artificial Ventilation: How, When and Why, 2014 ®

tilators may help identify leakage, for example, Vignaux et al. showed that the presence of ineffective breaths and the presence of delayed cycling were significantly associated with the magnitude of the leak. [4]

Most new-generation bilevel positive airway pressure devices estimate leaks automatically, which are displayed on the screen of the ventilator. The staff must be aware of the ideal leakage that could be obtained in the device, interface, and circuit used, whether the intentional leak is calculated together with unintentional leaks or not. Moreover, the type of circuit and expiratory valve may influence leak assessment: single circuits used in bilevel ventilators may be vented (with a calibrated intentional leak) or nonvented (with an expiratory valve). The latter circuit only provides information on the inspiratory tidal volume and cannot measure the expiratory tidal volume and hence the patient's real tidal volume during leaks. However, estimation of leaks performed by ventilator software is less precise when the leak increases. [1]

Two different types of circuits can be used to provide NIV: double circuit, in which inspiration and expiration are separated and an expiratory valve is present to prevent CO_2 rebreathing, or single-limb circuit, which does not have a true exhalation valve, so it includes an intentional leak to avoid rebreathing, either at the mask level or in the circuit. When monitoring NIV through waveforms, the mode of exhalation used and the

position of the flow sensor (concerning the expiratory device) both have a major influence on features of respiratory traces. In the case of a double circuit provided by an expiratory valve, the expiratory slope will be representative of the expiratory volume if the flow sensor is interposed between the mask and the exhalation device, but not when it is placed distally to the expiratory valve. Regarding a single circuit with an intentional leak, the expiratory slope does not reflect the expired tidal volume and the position of the flow sensor does not significantly change the expiratory slope. [8]

Zhu et al. proved that the adverse effects of leaks during the triggering phase vary according to not only the absolute leak level but also the mechanical properties of the lung and upper airway patency. According to different devices and clinical situations, the maximal leak level tolerated without inducing significant asynchrony must be determined. However, they also showed that without upper airway obstruction, all ventilators performed well with leaks lower than 30 L/min. This proved that modern home ventilators can avoid patient-ventilator asynchrony at a much higher level of leaks than previously reported. [10]

Several interventions may reduce air leaks, as using an appropriate interface type, with the correct size and headgear. If these are not enough to control air leaks, a small reduction of peak inspiratory pressure or switching from a volume-controlled to a pressure-targeted mode of ventilation can be tried. Conversely, increasing the pressure or tidal volume, depending on the ventilation mode, can improve minute ventilation despite the higher leakage, as long as the patient tolerates such a strategy. [9]

7.2.5 Monitoring Patient-Ventilator Asynchrony

The identification of patient-ventilator mismatch is often possible through observation of flow-volume waveforms. However, it requires expertise by the operator and close visual monitoring. Longhini et al. assessed the ability of intensive care unit physicians to recognize asynchronies during NIV by visual inspection of airway pressure (Paw) and flow-volume waveforms and they showed their ability in detecting severe asynchrony is low. Also, they proved that asynchrony detection was significantly higher with mask than with helmet. [3]

The creation of reliable software that would recognize major asynchronies would overcome these constraints. Mulqueeny et al. validated and tested a noninvasive method that automatically detects the occurrence of the major problems of patient-ventilator interaction in real-time, namely, ineffective and double triggering. Besides, no differences were observed in sensitivity and specificity during pressure-support ventilation and pressure-control ventilation, suggesting the reliability of the method under different conditions. [11] However, the variety of mismatching during NIV is probably higher and therefore the algorithm may underestimate the problem.

Severe asynchrony is characterized by an asynchrony index (AI) $\geqslant$10%, which is defined by the number of asynchrony events divided by the total respiratory rate, computed as the sum of the number of ventilator cycles (patient-triggered) and wasted efforts. [11]

Asynchronies are associated with different phases of the respiratory cycle: during inspiratory triggering (i.e., ineffective effort, double triggering, and auto-triggering) or cycling from inspiration to expiration (i.e., premature cycling). [8]

7.2.5.1 Auto-Triggering

Auto-triggering happens when the ventilator is triggered in the absence of a patient's effort. [5] It can be caused by patient movement, suctioning, coughing, and swallowing, and it is more likely to occur when the trigger sensitivity is set too high, especially if it is flow based. [7] Paw distortion due to circuit leaks, presence of water in the circuit, and cardiogenic oscillators can also be associated with this type of asynchrony. [5] Actually, in a multicenter study performed by Vignaux et al., they reported a higher magnitude of the leak in patients in whom auto-triggering

was present, although there was no correlation between leak volume and the severity of auto-triggering. [4]

Inspection of pressure and flow waveforms may help to identify auto-triggering: the absence of the initial pressure drop below end-expiratory pressure suggests auto-triggering. With flow triggering systems, however, the pressure drop before the mechanical breath may be minimal if the resistance upstream to the Paw measurement is very low, making the signal less clear. Also, the flowtime waveform of auto-triggered breaths may differ substantially from that triggered by the patient's inspiratory effort (see Fig. 7.2). [5]

7.2.5.2 Triggering Delay and Ineffective Effort

As mentioned above, PEEPi is related to dynamic hyperinflation and it has a negative impact on ventilator triggering because inspiratory flow only starts after PEEPi is counterbalanced, leading to a delay between the beginning of inspiratory effort and the triggering. In some cases, the inspiratory effort of the patient is not able to counterbalance PEEPi, resulting in the inability to trigger the ventilator-ineffective efforts. [5]

Inspection of flow curves may be highly suggestive: an abrupt decrease in expiratory flow happens, either when inspiratory muscle contracts or expiratory muscle relaxes if expiration is

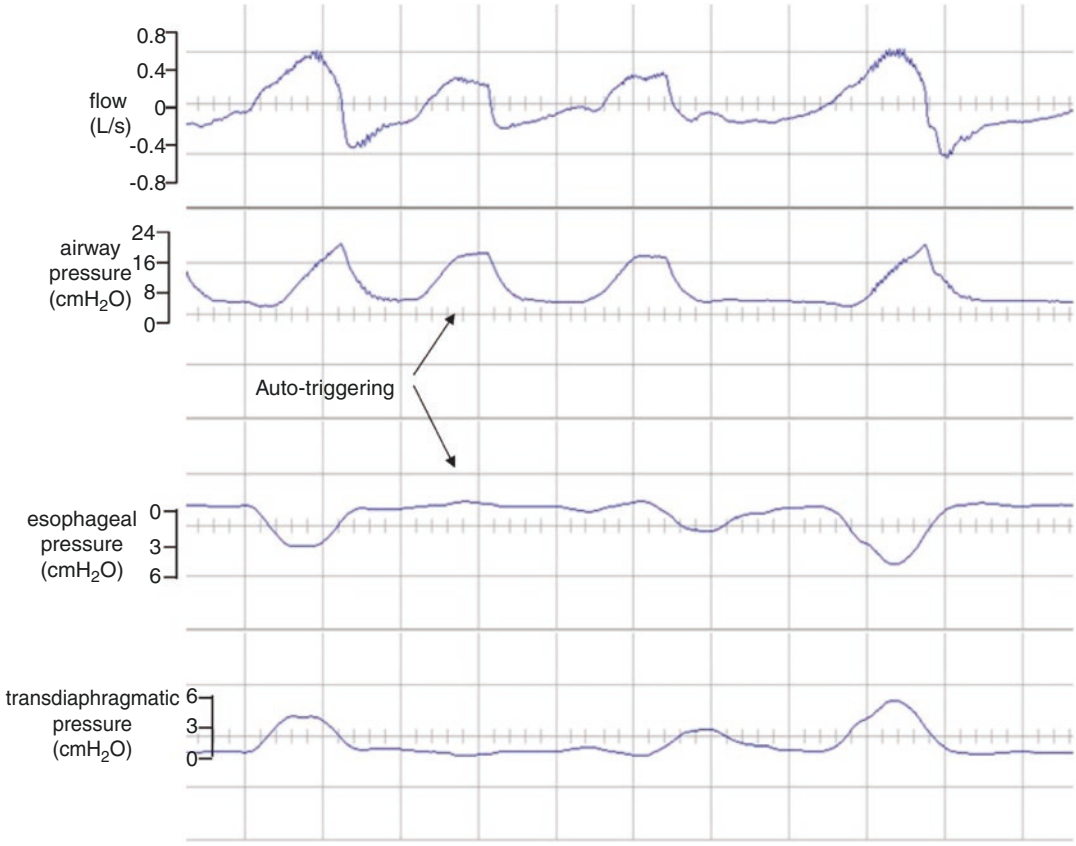

Fig. 7.2 Presence of auto-triggering: ventilator is triggered in the absence of a patient's effort (arrows), as it can be seen by the absence of pressure drop below end-expiratory pressure on esophageal waveform. Reprinted with permission from Springer: Nava and Fanfulla F, Non Invasive Artificial Ventilation: How, When and Why, 2014

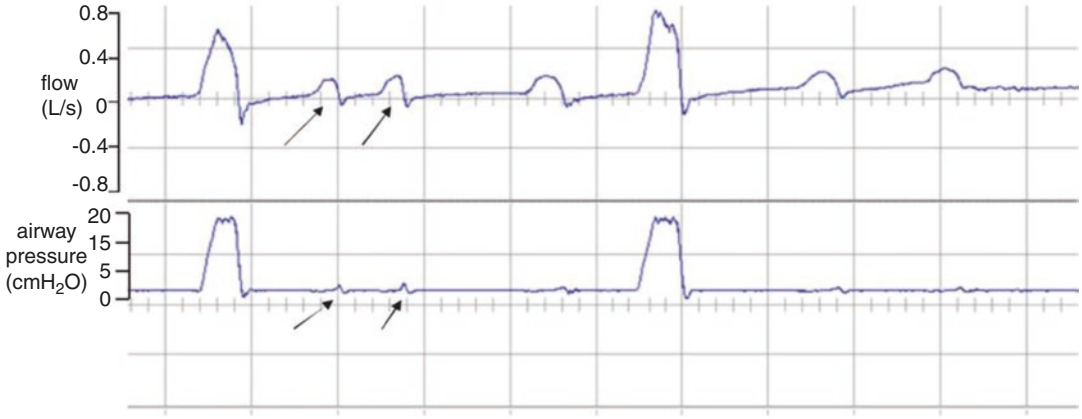

Fig. 7.3 Presence of ineffective efforts: decrease in the expiratory flow of the patient, not followed by ventilator support (arrows). Reprinted with permission from Springer: Nava and Fanfulla F, Non Invasive Artificial Ventilation: How, When and Why, 2014

active. Triggering delay is the period between the point of expiratory flow deviation (the beginning of the triggering phase) and the point at which Paw starts to increase. A decrease in the expiratory flow not followed by ventilator support is probably due to ineffective effort, which means that the patient is trying to trigger the ventilator, but was unsuccessful (see Fig. 7.3). [5]

To decrease the triggering delay and the number of ineffective efforts, there are some strategies, such as reducing the magnitude of dynamic hyperinflation (low tidal volume, long expiratory time), application of external PEEP, or decrease the threshold for triggering. [5]

7.2.5.3 Double Triggering

In the new algorithm proposed by Mulqueeny et al., double triggering was defined as two cycles separated by a very short expiratory time. [11]

It means that one inspiratory effort triggered the ventilator twice and is often associated with an insufficient level of pressure support in the face of increased inspiratory demand. [4] It can also be related to a high flow or a too sensitive expiratory trigger, leading to a transition from inspiration to expiration with a small flow fall.

7.2.5.4 Premature Cycling

Premature or short cycle happens when patient neural inspiratory time, determined from diaphragmatic electromyographic activity tracing, continues beyond the end of the ventilatory inspiratory time [1]. Although premature cycling is usually more associated with the presence of restrictive pulmonary pattern, Vignaux et al. reported a higher prevalence of this form of asynchrony in patients with acute community-acquired pneumonia. [4]

7.3 Conclusion Discussion

Patient tolerance to NIV, either in the setting of acute or chronic respiratory failure, depends directly on air leaks, which in turn are usually the cause of patient-ventilator asynchrony. The close observation of pressure, flow, and volume waveforms displayed in the monitor of ventilators may give some crucial information about patient-ventilator interaction. Also, waveform evaluation may give a clue about the respiratory system mechanics and the effectiveness of the treatment.

Key Major Recommendations

- The pressure, volume, and flow waveforms displayed in the monitor of new-generation ventilators are of great help in the identification of several aspects of patient-ventilator interaction.
- Monitorization of basic parameters during NIV, such as expiratory vital volume or the I:E

ratio, or identification of intrinsic positive end-expiratory pressure, is essential to achieve successful ventilation.
- Air leaks should be monitored because of their detrimental effect on the patient-ventilator interaction and the efficiency of NIV.
- The identification of patient-ventilator mismatch is often possible through observation of flow-volume waveforms.

References

1. Ergan B, Nasilowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev. 2018;27
2. Borel JC, Sabil A, Janssens JP, et al. Intentional leaks in industrial masks have a significant impact on efficacy of bilevel noninvasive ventilation. Chest. 2009;135:669–77.
3. Longhini F, Colombo D, Pisani L, et al. Efficacy of ventilator waveform observation for detection of patient–ventilator asynchrony during NIV: a multicentre study. ERJ Open Res. 2017;3:00075–2017.
4. Vignaux L, Lyazidi A, Cordoba-Izquierdo A, et al. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med. 2009;35:840–6.
5. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. Intensive Care Med. 2006;32:34–47.
6. Di Marco F, Centanni S, Bellone A, et al. Optimization of ventilator setting by flow and pressure waveforms analysis during noninvasive ventilation for acute exacerbations of COPD: a multicentric randomized controlled trial. Crit Care. 2011;15:R283.
7. Davidson C, Banham S, Elliott M, et al. BTS/ICS guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71
8. Rabec C, Rodenstein D, Leger P, et al. Ventilator modes and settings during non-invasive ventilation: effects on respiratory events and implications for their identification. Thorax. 2011;66:170–8.
9. Brill AK. How to avoid interface problems in acute noninvasive ventilation. Breathe. 2014;10:231–42.
10. Zhu K, Rabec C, Gonzalez-Bermejo J, et al. Combined effects of leaks, respiratory system properties and upper airway patency on the performance of home ventilators: a bench study. BMC Pulm Med. 2017;17:1–9.
11. Mulqueeny Q, Ceriana P, Carlucciet A, et al. Automatic detection of ineffective triggering and double triggering during mechanical ventilation. Intensive Care Med. 2007;33:2014–8.

8 Cough Evaluation: Measurement and Scores

Gil Gonçalves, Rafaela Cabral, and Bruno Cabrita

Abstract

Cough protects the lung from the inhalation of foreign materials and clears excessive bronchial secretions; and its impairment has been associated with increased respiratory infection rate, atelectasis, and respiratory failure.

In this chapter, we discuss ways to measure cough strength and its scores, as well as indications for cough-augmentation therapy.

Keywords

Cough · Cough evaluation · Cough impairment · Cough-augmentation therapy

Abbreviations

cmH_2O	Centimeter of water
COPD	Chronic obstructive pulmonary disease
L	Liter
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
NREM	Nonrapid eye movement
PCF	Peak cough flow
REM	Rapid eye movement
SNIP	Sniff nasal inspiratory pressure
VC	Vital capacity

G. Gonçalves (✉)
Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

R. Cabral
Family Health Unit, USF Viseu Cidade, Viseu, Portugal

B. Cabrita
Pulmonology Department, Hospital Pedro Hispano, Matosinhos, Portugal

8.1 Introduction

Cough is a physiologic mechanism that protects the lung from the inhalation of foreign materials and clears excessive bronchial and other secretions [1].

The act of cough consists of three phases: an inspiratory phase, where the patient inhales 60–90% of total lung capacity; a contraction phase, where the glottis closes for about 0.2 s and the abdominal and intercostal expiratory muscles begin to contract, which results in a significant intrathoracic pressure increase up to 50–300 cm of water (cmH_2O); and an expiratory phase where the glottis opens rapidly during 20–40 ms, generating a forceful airflow able to move secretions and trapped materials, particularly from the larger central airways. This generates an airflow of 360–1200 liters (L)/min in a healthy individual [1].

Cough impairment has been associated with increased respiratory infection rate, atelectasis, and respiratory failure. Weakness of inspiratory

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_8

muscles, mostly due to diaphragmatic weakness, prevents reaching high lung volumes and decreases cough effectiveness by putting the expiratory muscles at a mechanical disadvantage [2, 3]. This is a frequent finding in the heterogeneous group of neuromuscular diseases [2, 3].

Chest wall disorders, as significant thoracic scoliosis, can reduce lung and chest wall compliance values to about 25–50% of predicted. Scoliosis also reduces maximal inspiratory and expiratory pressures by an inefficient relationship between the thoracic cage and the respiratory muscles [3].

8.2 Discussion and Analysis of the Main Topic

8.2.1 Assessment of Cough Impairment

The most common measurements include vital capacity (VC), peak cough flow (PCF), and maximal inspiratory and expiratory pressures [3].

8.2.2 Vital Capacity

Vital capacity (VC) is evaluated in pulmonary function testing. The minimum volume for the generation of effective cough flow should be 50% of VC [4–6]. A low VC compromises the patient's breathing as well. When it is below this level, lung expansion is impaired and diffuse microatelectasis starts to appear. When it is between 40% and 60% of predicted, we start to observe rapid eye movement (REM)-related sleep-disordered breathing, and when between 20% and 40% of predicted, sleep-disordered breathing extends to nonrapid eye movement (NREM) sleep. Daytime ventilatory failure is observed when the VC is below 20% of predicted [2, 4].

The higher the VC, the higher the cough effectiveness, as the intrathoracic pressure increases when more volume is compressed against the closed glottis. A manual resuscitator is indicated in neuromuscular patients with a VC <2000 mL to improve lung compliance and assist cough technique [2, 3, 7].

Healthy individuals have a difference in VC from sitting to supine positions of 7.5% ± 5.7%. When this difference is >10%, it is often associated with diaphragmatic dysfunction, when >15% it is associated with unilateral diaphragmatic paresis, and when >25% it is associated with bilateral diaphragmatic paresis [2, 4].

8.2.3 Peak Cough Flow

Peak cough flow (PCF) is measured with a peak flow meter or a pneumotachometer. The patient is asked to inspire to total lung capacity and then forcibly cough, through either a face mask or a mouthpiece attached to the peak flow device. This test evaluates cough as a whole and cannot differentiate separate components of cough limitation [3, 7, 8].

PCF has the main advantage of an easy execution technique. PCF measured by a peak flow meter is a better and more reliable measurement of expiratory muscle strength in patients with muscular weakness, in whom effort-related test reproducibility is often difficult [8].

PCF magnitude determines the ability to eliminate respiratory secretions during a cough [3]. Normal individuals may produce a PCF as great as 720 L/min (occasionally higher in healthy individuals). A PCF above 270 L/min indicates effective cough, whereas a PCF less than 160 L/min identifies patients with ineffective cough. Patients with a PCF between 160 and 270 L/min are at higher risk of respiratory tract infections, which can further reduce muscle strength. In individuals unable to achieve and maintain efficient cough flow to remove these increased secretions, assisted cough can reduce morbidity and mortality [7–9].

8.2.4 Maximal Inspiratory Pressure and Maximal Expiratory Pressure

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are recommended for monitoring respiratory strength. They are measured by strongly urging patients to make

maximum inspiratory (Mueller maneuver) and expiratory (Valsalva maneuver) efforts at or near residual volume and total lung capacity, respectively, against a closed shutter [2, 3].

Both values are higher in men and decrease with aging. A clearly reduced MIP or MEP, not related to poor effort or technique, suggests respiratory muscle weakness, which includes neuromuscular diseases and systemic conditions that affect skeletal muscle strength. Most chronic obstructive pulmonary disease (COPD) patients do not have respiratory muscle weakness, but have reduced MIP due to hyperinflation which shortens the inspiratory muscles [2, 3, 10].

A MIP value >80 cmH_2O excludes clinically important inspiratory muscle weakness and a MEP >90 cmH_2O excludes expiratory muscle weakness. MEP <60 cmH_2O is indicative of an ineffective cough [2, 3, 10].

8.2.5 Other Techniques

Sniff nasal inspiratory pressure (SNIP) is a noninvasive test of inspiratory muscle strength. Advantages include the simplicity of the maneuver, portability, and low cost. With a bung into one nostril through which a thin catheter connected to a pressure transducer has been passed, the patient is instructed to sniff as strongly as possible through the contralateral unobstructed nostril. The pressure measured in the obstructed nostril is an indicator of inspiratory muscle strength. It is sensitive in the precocious detection of inspiratory muscle weakness. A SNIP value >70 cmH_2O in men and >60 cmH_2O in woman excludes significant inspiratory muscle weakness. A value <30 cmH_2O is indicative of cough impairment [2, 3].

Invasive tests (breathing pattern with esophageal and gastric pressure; esophageal pressure and transdiaphragmatic pressure during a maximal sniff; and gastric pressure during a maximal cough) require the placement of esophageal and gastric balloon catheters, which limits their routine monitoring use to centers with expertise [2, 3].

8.2.6 Indications to Start Cough-Augmentation Therapies

Cough-augmentation therapies, which include, but are not limited to, (1) manual or mechanical insufflation, (2) breath/air stacking, (3) glossopharyngeal breathing, (4) mechanical insufflation-exsufflation, (5) mechanical exsufflation, and (6) manually assisted cough, are indicated when the patient cannot produce an effective cough [2, 8].

Studies have identified a PCF of 160 L/min as the threshold value for mandatory start of cough-augmentation therapy; however, a PCF between 160 and 270 L/min could fall below 160 L/min during a pulmonary decompensation. For this reason, it is recommended to start cough-augmentation therapy when the PCF falls below 270 L/min [3, 9].

Other indications include MEP <60 cmH_2O and a history of repeated respiratory infections [2, 3, 10].

Contraindications to mechanical insufflation-exsufflation include a history of bullous emphysema, known susceptibility to pneumothorax or pneumomediastinum, and recent barotrauma [8].

8.3 Conclusion Discussion

Cough impairment has been associated with a high risk of developing respiratory complications, including atelectasis, pneumonias, and respiratory insufficiency. Respiratory tests are important tools to help evaluate the respiratory status and cough efficiency, as well as to monitor disease progression and aid in prognosis.

Common tests to assess cough impairment include VC, PCF, MIP, MEP, and SNIP. These tests are unexpensive, easy to perform, and widely available.

These tests are usually decreased in comparison to a healthy population. Certain threshold values have been identified to guide clinicians in deciding when to initiate further treatments, including cough-augmentation therapies, or further testing.

Values of VC <50% of predicted, PCF <270 L/min, MEP <60 cmH_2O, and a SNIP value <30 cmH_2O are indicative of cough impairment.

Key Major Recommendations

- Cough protects the lung from the inhalation of foreign materials and clears excessive bronchial secretions.
- Cough impairment has been associated with increased respiratory infection rate, atelectasis, and respiratory failure.
- Low values of VC, PCF, MIP, MEP, and SNIP are associated with cough impairment.
- Indications for cough-augmentation therapy include a PCF <270 L/min, MEP <60 cmH_2O, and a history of repeated respiratory infections.

References

1. Polverino M, Polverino F, Fasolino M, Ando F, Alfieri A, De Blasio F. Anatomy and neuro-pathophysiology of the cough reflex arc. Multidiscip Respir Med. 2012;7(1):5.
2. Finder JD, Birnkrant D, Carl J, Farber HJ, Gozal D, Iannaccone ST, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med. 2004;170(4):456–65.
3. Camela F, Gallucci M, Ricci G. Cough and airway clearance in Duchenne muscular dystrophy. Paediatr Respir Rev. 2019;31:35–9.
4. Kang SW, Bach JR. Maximum insufflation capacity. Chest. 2000;118(1):61–5.
5. Mellies U, Goebel C. Optimum insufflation capacity and peak cough flow in neuromuscular disorders. Ann Am Thorac Soc. 2014;11(10):1560–8.
6. Kang SW, Kang YS, Sohn HS, Park JH, Moon JH. Respiratory muscle strength and cough capacity in patients with Duchenne muscular dystrophy. Yonsei Med J. 2006;47(2):184–90.
7. Sferrazza Papa GF, Pellegrino GM, Shaikh H, Lax A, Lorini L, Corbo M. Respiratory muscle testing in amyotrophic lateral sclerosis: a practical approach. Minerva Med. 2018;109(6 Suppl 1):11–9.
8. Jung JH, Oh HJ, Lee JW, Suh MR, Park J, Choi WA, et al. Improvement of peak cough flow after the application of a mechanical in-exsufflator in patients with neuromuscular disease and pneumonia: a pilot study. Ann Rehabil Med. 2018;42(6):833–7.
9. Bianchi C, Baiardi P. Cough peak flows: standard values for children and adolescents. Am J Phys Med Rehabil. 2008;87(6):461–7.
10. Chiang J, Mehta K, Amin R. Respiratory diagnostic tools in neuromuscular disease. Children (Basel). 2018;5(6)

Gas Exchange

9

Eleni N. Sertaridou and Vasilios E. Papaioannou

Abstract

Oxygen delivery (DO_2) from the atmosphere into tissues is a complex process that includes ventilation, oxygen transport from the alveoli to the blood, hemoglobin's (Hb's) affinity for oxygen, the cardiac output (CO), the oxygen saturation in blood, and the distribution of tissue supply. Understanding this process finds practical application in critically ill patients' treatment, as it allows identifying the problem and taking corrective action.

Keywords

Arterial blood gases · Pulmonary gas exchange · Oxygen delivery · Oxygen consumption

Abbreviations

A	Alveolar
A	Surface area of the tissue
ABG	Arterial blood gases
ARDS	Acute respiratory distress syndrome
BP	Barometric pressure
C	Concentration
C_{aO2}	Systemic arterial oxygen concentration
$C_{a\text{-}v}O_2$	Arterio-Venous difference oxygen concentration
C_{H2O}	Water vapor concentration
C_{N2}	Nitrogen concentration
CO	Cardiac output
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
C_{pvO2}	Pulmonary venous oxygen concentration
C_{VO2}	Pulmonary arterial oxygen concentration
D	Delivery
D	Diffusion coefficient
D_{LO2}	Lung's diffused capability
F	Fractional concentration
F_{AO2}	Oxygen concentration in alveolar air
F_{ECO2}	Carbon dioxide concentration in expired air
F_{EO2}	Oxygen concentration in expired air
F_{iCO2}	Carbon dioxide concentration in inspired air
F_{iO2}	Oxygen concentration in inspired air
Hb	Hemoglobin
HbO_2	Oxyhemoglobin
κ	A constant
m^2	Square meters

E. N. Sertaridou (✉) · V. E. Papaioannou
Intensive Care Unit,
University Hospital of Alexandroupolis,
Alexandroupoli, Greece

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_9

min	minute
mm Hg	Millimeter of mercury
MW	Molecular weight
N_2	Nitrogen
O_2	Oxygen
O_2ER	Oxygen extraction ratio
P	Partial pressure
$P_{A-a}O_2$	Alveolar-arterial oxygen partial pressure difference
P_{ACO2}	Alveolar carbon dioxide partial pressure
$P_{A-C}O_2$	Alveolar-capillary oxygen partial pressure difference
P_{AO2}	Alveolar oxygen partial pressure
$P_{arterialCO2}$, P_{aCO2}	Arterial carbon dioxide partial pressure
$P_{arterialO2}$, P_{aO2}	Arterial oxygen partial pressure
P_{atm}	Atmospheric pressure
P_{CO2}	Carbon dioxide partial pressure
P_{cO2}	Partial pressure of oxygen in capillaries' blood
P_{ECO2}	Mixed expired carbon dioxide
PEEP	Positive end-expiratory pressure
P_{EO2}	Mixed expired oxygen
P_{H2O}	Water vapor partial pressure
$P_{inspiredO2}$, P_{iO2}	Oxygen partial pressure in inspired air
P_{O2}	Oxygen partial pressure
P_{tCO2}	Tissue carbon dioxide partial pressure
P_{tO2}	Tissue oxygen partial pressure
P_{total}	Total pressure
Q	Lung perfusion (pulmonary blood flow)
RQ	Respiratory quotient
S_{aO2}	Arterial blood oxygen saturation
Sol	Gas solubility
S_{vO2}	Mixed venous blood oxygen saturation
T	Tissue thickness
V'_{gas}	Rate of a gas diffusion
VA	Alveolar ventilation
V_{CO2}	Ratio of the produced carbon dioxide
VD	Ventilation of the dead space
V_E	Per minute expired air volume
V_I	Per minute inspired air volume
VO_2	Ratio of the consumed O_2
V_{total}	Total ventilation
ΔP	Drastic partial pressure difference of oxygen in the alveoli versus the pulmonary capillaries' blood
μm	Micrometer

9.1 Introduction

The purpose of the respiratory system is to perform gas exchange, oxygen (O_2) absorption from inhaled air, tissue supply, and carbon dioxide (CO_2) removal. To this end, the following functions take place [1]:

- Pulmonary ventilation provides air to the alveoli.
- At the respiratory membrane, where the alveolar and capillary walls meet, gases move across very thin membranes, with O_2 entering the bloodstream and CO_2 exiting.
- Blood oxygenates tissue and cells and removes CO_2 and waste products from the body tissues.
- Perfusion.

In order to understand the gas exchange mechanism in the lung, it is important to analyze the underlying principles of gases and their behavior [2].

9.2 Discussion and Analysis of the Main Topic

9.2.1 General Physics Principles: Definitions

All gases participating in respiratory physiology are small molecules moving freely along concentration gradients. The exchange of gases between

the alveoli and the blood occurs by simple passive ***diffusion.*** There is no active transport involved in alveolar gas exchange, while both ventilation and perfusion are convective processes that require energy expenditure and in cardiorespiratory diseases may be compromised [2].

Gas molecules exert force (pressure) on the surfaces with which they are in contact. In natural systems, gases are present as a mixture of different types of molecules. ***Partial Pressure (P)*** is the pressure of a single type of gas in a mixture of gases, while according to Dalton's law a specific gas type in a mixture exerts its own pressure; thus, the ***Total Pressure (P_{total})*** exerted by a mixture of gases is the sum of all the partial pressures of the gases in the mixture. The total pressure is directly proportional to the concentration of the total gas molecules. Partial pressure is important in predicting the movement of gases. Gases tend to equalize their pressure in two regions that are connected. A gas will move from an area where its partial pressure is higher to an area where it is lower. In addition, the greater the partial pressure difference between the two areas, the more rapid is the movement of gases [2].

The atmosphere, the principal inspirational gaseous mixture, consists of 79% nitrogen (N_2), 21% oxygen (O_2), 0.04% carbon dioxide (CO_2), and other gaseous molecules in smaller concentrations (Table 9.1). This gaseous mixture exerts a certain pressure referred to as atmospheric pressure (P_{atm}). The total atmospheric pressure on the level of sea surface is P_{atm} = 740 mm Hg (millimeters of mercury):

$$P_{atm} = P_{N2} + P_{O2} \quad (9.1)$$

where the partial pressure of nitrogen (P_{N2}) = 79% × 740 mm Hg = 600 mm Hg and the partial pressure of oxygen (P_{O2}) = 21% × 740 mm Hg = 160 mm Hg.

On the other hand, Henry's law describes the behavior of gases when they come into contact with a liquid, such as blood. It states that the concentration of a gas in a liquid is directly proportional to the solubility and the partial pressure of that gas. For example, although N_2 is present in the atmosphere, very little N_2 dissolves into the blood, because its solubility in the blood is very low (Table 9.2) [2].

The composition of air in the atmosphere and in the alveoli differs. In both cases, the relative concentration (C) of gases is $C_{N2} > C_{O2}$ > water vapor (C_{H2O}) > C_{CO2}. The amount of water vapor present in alveolar air is greater than that in atmospheric air (Table 9.1). Recall that the respiratory system works to humidify incoming air, thereby causing the air present in the alveoli to have a greater amount of water vapor than atmospheric air. Furthermore, alveolar air contains a greater amount of CO_2 and less O_2 than atmospheric air, as the gas exchange removes O_2 from and adds CO_2 to alveolar air. Both deep and forced breathing cause the alveolar air composition to be

Table 9.2 Solubility contributors of main respiratory gases

Oxygen (O_2)	0.024
Carbon dioxide (CO_2)	0.57
Carbon monoxide (CO)	0.018
Nitrogen (N_2)	0.012
Helium (he)	0.008

Table 9.1 Composition and partial pressure of atmospheric and alveolar air

	Alveolar air	Atmospheric air		
Gas	Percentage of total composition (%)	Partial pressure (mm Hg)	Percentage of total composition (%)	Partial pressure (mm Hg)
Nitrogen (N_2)	74.9	569	78.08	597.4
Oxygen (O_2)	13.7	104	20.95	158.8
Water vapor (H_2O)	6.2	40	0.00001–4.0	3.0
Carbon dioxide (CO_2)	5.2	47	0.0360	0.3

changed more rapidly than during shallow and rapid breathing. As a result, the partial pressures of oxygen (P_{O2}) and carbon dioxide (P_{CO2}) change, affecting the diffusion process that moves these materials across the membrane. This will cause O_2 to enter and CO_2 to leave the blood more quickly [1].

The diffusion of gases across tissues is governed by Fick's law, according to which the rate of diffusion (V'_{gas}) of a gas through a tissue layer is proportional to the surface area of the tissue (*A*), the diffusion coefficient (D), and the difference of the partial pressure between both sides (P_1–P_2) and inversely proportional to the tissue thickness (T):

$$V'_{gas} = A / T \times D \times \left(P_1 - P_2\right) \tag{9.2}$$

$$D = \frac{Sol}{\sqrt{MW}} \tag{9.3}$$

where D: diffusion coefficient, Sol: gas solubility, and MW: molecular weight.

The surface area of separating membrane between the alveolar space and the blood measures 50–100 m^2 and its thickness is 0.3 μm. The diffusion coefficient is proportional to a constant that depends on the characteristics of the tissue and the gas. In particular, this constant is directly proportional to the gas solubility and inversely proportional to the square root of its molecular weight. Although the molecular weights of O_2 and CO_2 are not much different, CO_2 diffuses 20 times faster than O_2, because of its greater solubility [3].

The partial pressure of each gas in the mixture of respiratory gases tends to push the gas molecules toward the alveolar membrane and subsequently to the capillary blood. The direction of diffusion is determined by the difference between both pressures. If the partial pressure is greater in the gas phase more molecules will move into the solution, while if the partial pressure within the blood is greater, then the gas diffuses toward the alveoli [1].

9.2.2 Ventilation and Perfusion

Ventilation, the movement of air into and out the lungs, and perfusion, the flow of blood in the pulmonary capillaries, are the main aspects of gas exchange in the lung. Volumes involved in ventilation and perfusion should be compatible, in order for gas exchange to be efficient. Normally, all alveoli are both ventilated and perfused. However, even in health, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion imbalance.

The passage of the atmospheric air through the respiratory tract until the lungs results in its saturation in water vapor. The atmospheric air saturation of water vapor reduces O_2 partial pressure in inspired air ($P_{inspiredO2}$, P_{iO2}).

$$P_{iO2} = \left(BP - P_{H2O}\right) \times F_{iO2} \tag{9.4}$$

P_{H2O} is the partial pressure of water vapor at 37°C, at sea level it is 47 mm Hg and P_{iO2} at sea level is: $P_{iO2} = (760–47) \times 0.21 = 149$ mm Hg, BP is the barometric pressure, and F_{iO2} is oxygen concentration in inspired air.

Alveolar oxygen partial pressure (P_{AO2}, A = Alveolar) is difficult to be measured directly. The "ideal" P_{AO2}:

$$P_{AO2} = P_{inspiredO2} - P_{arterialCO2} \tag{9.5}$$

Equation (9.5) is based on the presumption that ventilation and perfusion disturbances result in small differences between arterial and alveolar CO_2 partial pressure ($P_{aCO2} - P_{ACO2}$), and provides a rough estimation of P_{AO2}. Its accuracy is limited because:

- CO_2 removal is less than inspired O_2.
- Inspired volume is not equal to expired [5].

The equation can be modified:

$$P_{AO2} = P_{iO2} - P_{aCO2} / RQ \tag{9.6}$$

P_{aCO2} is the arterial CO_2 partial pressure and RQ the respiratory quotient, meaning the ratio of the produced CO_2 (V_{CO2}) to the consumed O_2 (V_{O2}) (usually ~0.8):

$$RQ = V_{CO2} / V_{O2} \tag{9.7}$$

if P_{ACO2} = 40 mm Hg and P_{AO2} = 150 – 40/0.8 = 100 mm Hg.

The most reliable equation that counts alveolar O_2 was proposed by Filley et al. in 1954 [6]:

$$P_{AO2} = P_{iO2} - P_{ACO2} \times \left(P_{iO2} - P_{EO2} / P_{ECO2}\right) \quad (9.8)$$

P_{EO2} is the mixed expired O_2 and P_{ECO2} the mixed expired CO_2. In this equation, RQ is not required. If in Eq. (9.6), RQ is replaced according to Eq. (9.7), then:

$$P_{aCO2} = \kappa V_{CO2} / VA \quad (9.9)$$

where κ is a constant, V_{CO2} the produced CO_2, and VA the alveolar ventilation.

$$VA = V_{total} - VD \quad (9.10)$$

V_{total} is the total ventilation and VD the ventilation of the dead space,

$$P_{AO2} = \left(BP - P_{H2O}\right) \times F_{iO2} - V_{O2} / VA \quad (9.11)$$

while BP is the barometric pressure. The main factors that affect P_{AO2} are BP, F_{iO2}, the consumed O_2 (V_{O2}), the produced CO_2 (V_{CO2}), and alveolar ventilation (V_A). V_{O2} rises in pain, fever, increased work of breathing, seizures, and shiver. On the contrary, V_{O2} falls during anesthesia and hypothermia. When V_{O2} demands for ventilation are increasing, in order to maintain PAO2 in normal rates, the relation between alveolar ventilation and P_{AO2} is determined by the following equation:

$$P_{AO2} = P_{iO2} - V_{O2} / VA \quad (9.12)$$

It depicts a hyperbolic curve. When ventilation is raised, P_{AO2} is also increased to less than P_{iO2}. On the other hand, ventilation reduction causes serious results: P_{AO2} falls to very low levels, while in severe hypoventilation, it is also eliminated [5].

The P_{AO2} is 104 mm Hg, whereas the P_{O2} of the oxygenated pulmonary venous blood is 100 mm Hg. Sufficient ventilation preserves a high rate of O_2 alveoli entrance, while when ventilation is insufficient, P_{AO2} drops and O_2 diffusion across respiratory membrane is minimized. In these cases, blood flow is redirected to alveoli that have sufficient ventilation (shunt). Factors such as CO_2, O_2, and pH levels can serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli [5].

Ventilation is regulated by the airways' diameter, whereas perfusion by the blood vessels' diameter. The bronchioles' diameter is sensitive to the P_{ACO2}. A greater P_{ACO2} causes the bronchioles to increase their diameter similarly with decreased level of O_2 in blood supply, allowing CO_2 to be exhaled at a greater rate. A greater P_{AO2} causes dilation to the pulmonary arterioles, increasing subsequently, blood flow [1, 7].

9.2.3 Gas Exchange

Gas exchange occurs due to simple diffusion and pressure gradients, at two sites: in the alveoli, where O_2 is picked up by the erythrocytes and CO_2 is released through respiratory membrane, and at the level of peripheral tissues. External respiration is the exchange of gases with the external environment and occurs in the alveoli of the lungs. Internal respiration is the exchange of gases with the internal environment and occurs in the tissues [1].

9.2.4 External Respiration

The lungs are a collection of 300 million gas-filled polyhedrons (alveoli), the walls of which are made up of little more than a rich capillary network, supported by a very thin intestinal matrix [2]. This anatomy of the lung maximizes the diffusion of gases: The respiratory membrane is highly permeable to gases; the respiratory and blood capillary membranes are very thin (0.5–0.6 μm) and extended on a large surface area throughout the lungs (approximately 100–140 m^2) [4]. Respiratory membrane is composed of the squamous alveolar epithelial cell, the squamous pulmonary capillary endothelial cell, and their fused base membranes. Each alveolus expands with inspiration of gas (high in O_2 and low in CO_2 concentration) that has flowed down the bronchial tree from the mouth during inspiration. The alveoli then reduced in volume during expiration, returning gas (lower in O_2 and higher

in CO_2) through the bronchial tree to the mouth [2, 3].

The pulmonary artery carries deoxygenated blood into the lungs from the heart, where it repeatedly bifurcates into arterioles and capillaries that cover 85–95% of the alveolar surface, forming the capillary network composed of pulmonary capillaries, which are components of the respiratory membrane [4]. As the blood is pumped through this capillary network, gas exchange occurs, as a function of partial pressure differences in O_2 and CO_2 between the alveoli and the pulmonary capillaries' blood. Due to the relatively large blood volume within the alveolar capillaries, blood flow slows and the transit time for blood decreases, normally around 0.25–0.75 s, allowing more time for gas exchange. Although a small amount of O_2 is able to dissolve directly into plasma from the alveoli, most of it is picked up by erythrocytes and binds to hemoglobin, while CO_2 is released in the opposite direction, toward the alveoli. Oxygenated blood then returns to the heart through the pulmonary veins. A small portion of the CO_2 is returned to hemoglobin, but can also be dissolved in plasma or is present in a converted form [4].

Although the solubility of O_2 in blood is not high, there is a drastic partial pressure difference of O_2 ($\Delta P = 64$ mm Hg) in the alveoli versus the pulmonary capillaries' blood: $P_{AO2} = 104$ mm Hg, whereas partial pressure in the blood of the capillary is $P_{cO2} = 40$ mm Hg. This pressure gradient causes rapid O_2 diffusion through respiratory membrane from alveoli into the blood cell. Bohr's equation defines the connection between O_2 consumption (V_{O2}) and lung's diffused capability (D_{LO2}):

$$V_{O2} = \left(P_{AO2} - P_{cO2}\right) \times D_{LO2} \tag{9.13}$$

D_{LO2}: lung's diffused capability. This equation shows that the alveolar-capillary oxygen partial pressure difference ($P_{A-C}O_2$) is dependent on the lung's diffused capability.

Oxygen partial pressure in arterial blood (P_{aO2}) is less than P_{AO2}, while the alveolar-capillary difference $P_{A-C}O_2$ is defined by the following equation:

$$P_{A-a}O_2 = P_{AO2} - P_{aO2} \tag{9.14}$$

The alveolar-capillary difference ($P_{A-C}O_2$) can be easily estimated and used as a marker of respiratory disturbance. Normally, alveolar-arterial difference ($P_{A-a}O_2$) is less than 10 mm Hg and attributed to anatomic shunt between pulmonary and systematic circulation. Furthermore, naturally a few V/Q disturbances exist, causing $P_{A-a}O_2$ to increase (functional shunt).

There is also a smaller pressure gradient of CO_2 (around 5 mm Hg) between the alveolar air and blood cells: the partial pressure in blood is 45 mm Hg, whereas $P_{ACO2} = 40$ mm Hg. However, the solubility of CO_2 is much greater than that of O_2 (about 20 times), in both blood and alveolar fluids. As a result, the relative concentrations of O_2 and CO_2 that diffuse across the respiratory membrane are similar.

9.2.5 V/Q Disturbances

V/Q ratio is not homogeneous across the entire lung surface. Ventilation is higher at the level of lung's apexes in relation to lung's bases, while lung perfusion (Q) is reduced from bases to apexes. Lung perfusion is related to the body position and can be attributed to pulmonary vessels' hydrostatic pressure distinction. V/Q rises exponentially from lung's bases to apexes and can be affected by alveolar gases (P_{AO2}, P_{ACO2}). P_{AO2} diminution of hypoventilated regions ($V/Q < 1$) results in hypoxic pulmonary vasoconstriction, V/Q improvement, and venous admixture reduction. Hypocapnic bronchoconstriction is another balancing mechanism for V/Q ratio abnormalities. In hypoperfusioned regions ($V/Q > 1$) P_{ACO2} falls, causing bronchoconstriction and local hypoventilation, minimizing dead space ventilation [4].

The product of minute ventilation (V_E, L/min) and the difference between inspired (F_{iO2}) and mixed expired O_2 concentrations (F_{EO2}) quantifies the amount of O_2 (V_{O2}, L/min) that leaves the alveolar gas and enters the pulmonary capillary blood per minute (O_2 flow). The O_2 entering the pulmonary capillaries is quantified by the prod-

uct of pulmonary blood flow (Q, L/min) and the difference between pulmonary venous (C_{pvO2}, mL/dL) and pulmonary arterial (C_{vO2}, mL/dL) O_2 concentrations. Assuming that the lungs are homogeneous, the concentration of O_2 in the blood leaving every alveolus is the same, and passing unchanged into the systemic arterial blood, is equal to the systemic arterial O_2 concentration (C_{aO2}, mL/dL) [8]. This can be expressed by the following mass conservation equations:

$$V_{O2} = V_E \times \left(F_{iO2} - F_{EO2}\right) = V_A \times \left(F_{iO2} - F_{AO2}\right) \quad (9.15)$$

In the right-hand side of Eq. (9.15), it is recognized that the conducting airways do not themselves take part in air/blood gas exchange. This allows minute ventilation and mixed expired O_2 concentration to be replaced by alveolar ventilation (V_A) and alveolar O_2 concentration (F_{AO2}), respectively. Because the process of diffusional transport described above usually comes to rapid completion well within the red cell transit time (at rest at sea level), P_{O2} in the alveolar gas (P_{AO2}, mm Hg) and the capillary blood leaving the alveoli can be considered to be the same (Fig. 9.1). Furthermore,

$$V_{O2} = Q\left(C_{cO2} - C_{vO2}\right) \quad (9.16)$$

while,

$$V \times \left(F_{iO2} - F_{AO2}\right) = Q \times \left(C_{aO2} - C_{vO2}\right) \quad (9.17)$$

$$V / Q = \left(C_{cO2} - C_{vO2}\right) / \left(F_{iO2} - F_{eO2}\right) \quad (9.18)$$

and

$$V / Q = \left(C_{vCO2} - C_{cCO2}\right) / \left(F_{eCO2} - F_{iCO2}\right) \quad (9.19)$$

Rearranging the terms gives:

$$V / Q = 8.63 \times \left(C_{aO2} - C_{vO2}\right) / \left(P_{IO2} - P_{AO2}\right) \quad (9.20)$$

In the preceding section, some simplifying assumptions have been made. We assumed ventilation and perfusion are continuous processes, implying blood and gas O_2 concentrations are constant in time, thus ignoring the normal, minor fluctuations in alveolar P_{O2} between inspiration and expiration. We also assumed that the lung is homogeneous, with all alveoli having the same V/Q ratio; that inspired and expired gas volumes are identical, which is true to within 1%; and that

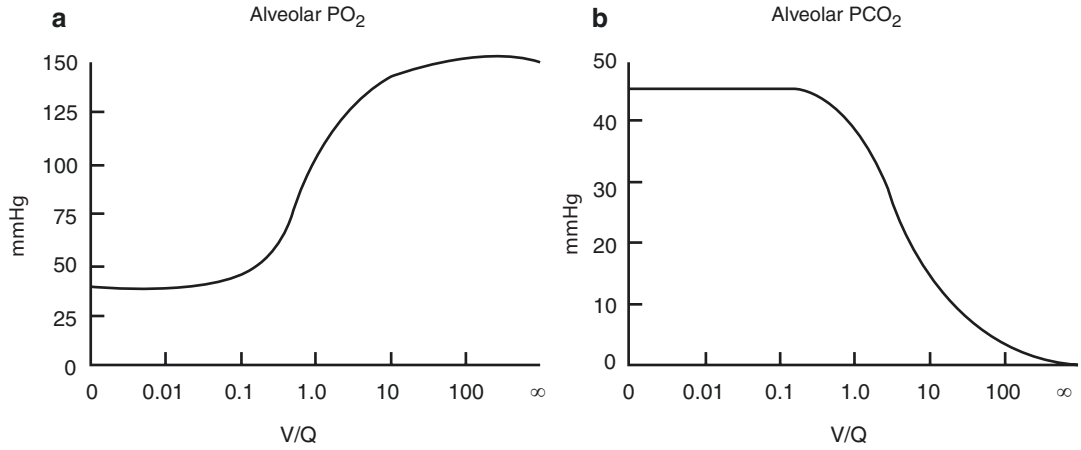

Fig. 9.1 P_{AO2} and P_{ACO2} relevance with V/Q. (**a**) O_2 diffusion from lungs toward blood is decreased, when V/Q is reduced 10 times (0.1), although further V/Q reduction slightly affects O_2 delivery (DO_2). V/Q increasing over the level of 1 slightly affects DO_2. (**b**) The alveolar P_{CO2} curve has opposite direction in comparison to the P_{AO2} curve. V/Q discretion from 1 to 0.1 slightly affects CO_2 removal, while its increase induces a great CO_2 reduction. This difference between the two curves is attributed to the differences in their dissociation curve gradient. Carbon dioxide's dissociation gradient is 10 times oxygen's gradient. Gases that have higher detachment gradient or solubility are more sensitive in higher values of V/Q. On the contrary, gases with lower detachment gradient or solubility are more sensitive in lower values of V/Q

the blood leaving the alveoli and entering the pulmonary veins reaches the systemic arteries (where it can be sampled clinically) without change in C_{aO2} (arterial blood O_2 concentration). Finally, diffusion equilibration has been assumed, allowing C_{aO2} to be directly calculated from the oxyhemoglobin (HbO_2) dissociation curve, if P_{AO2} is known.

Following through the exactly same logic presented for O_2, the equation for CO_2 is [8]:

$$V/Q = 8.63 \times \left(C_{vCO2} - C_{aCO2}\right) / \left(P_{ACO2} - P_{iCO2}\right) \quad (9.21)$$

The terms on the right-hand side for CO_2 are reversed (compared to O_2) only because CO_2 is being eliminated from the blood while O_2 is being taken up. This keeps both the numerator and the denominator of Eq. (9.21) positive. If a region of lung becomes poorly ventilated, due to airway obstruction (for example, in atelectasis), but still remains adequately perfused, the V/Q ratio of that region must be reduced, and subsequently, P_{AO2} and blood O_2 concentration will fall (while P_{ACO2} will rise by a small amount). Conversely, as V/Q rises in a lung region due to vascular obstruction (for example, during pulmonary embolism), P_{AO2} rises while P_{ACO2} falls. In this case, O_2 concentration rises a little, but P_{ACO2} and CO_2 concentration fall considerably. As a conclusion, when low V/Q ratio regions exist, O_2 is seriously affected, more so than CO_2, but when high V/Q ratio areas occur, CO_2 is the more affected gas [4].

According to Eq. (9.15):

$$V_{CO2} = V_A \times \left(F_{ACO2} - F_{iCO2}\right) \quad (9.22)$$

If Eq. (9.22) is divided by Eq. (9.15), and ignoring F_{iCO2} as negligible:

$$V_{CO2}/V_{O2} = RQ = F_{ACO2} / \left(F_{iO2} - F_{AO2}\right) = P_{ACO2} / \left(P_{iO2} - P_{AO2}\right) \quad (9.23)$$

RQ is by definition the respiratory quotient, and the change from fractional concentration (F) to partial pressure (P) follows Dalton's law of partial pressures. Proportionally:

$$P_{AO2} = P_{iO2} - P_{ACO2} / RQ \quad (9.24)$$

To be accurate and eliminate the assumption that the inspired and expired ventilation values are identical, Eq. (9.24) is modified:

$$P_{AO2} = P_{iO2} - P_{ACO2} / RQ + P_{ACO2} \times F_{iO2} \times \left(1 - RQ\right) / RQ \quad (9.25)$$

9.2.6 Internal Respiration

Internal respiration is the gas exchange that occurs at the level of body tissues. Similar to external respiration, it also occurs through simple diffusion due to a partial pressure gradient, which however is opposite to the gradient present at the respiratory membrane. The oxygen's partial pressure in tissues is low (about 40 mm Hg), because O_2 is continuously used for cellular respiration. Since the arterial oxygen partial pressure (P_{aO2}) = 100 mm Hg, pressure gradient is produced which causes O_2 dissociation from hemoglobin, diffusion through the endothelial layer toward the interstitial space and finally, entrance in the tissues [9].

Considering that cellular respiration continuously produces CO_2, the partial pressure of CO_2 is lower in the blood than it is in the tissue, causing CO_2 to diffuse out of the tissue, cross the interstitial fluid, and enter the blood. It is then carried back to the lungs either bound to hemoglobin, dissolved in plasma or in a converted form. By the time blood returns to the heart, the partial pressure of O_2 has returned to 40 mm Hg and the partial pressure of CO_2 to 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration [9, 10].

From the total amount of O_2 providing to the tissues, only a small part, according to metabolic needs, is committed. The O_2 amount, which is consumed by the tissues per minute, is known as O_2 consumption (VO_2). VO_2 can be counted either with Fick's law or with indirect calorimetric technique. According to Fick's law, cardiac output (CO) is equal to the quotient of O_2 con-

sumption (VO_2) toward the arteriovenous difference ($C_{a\text{-}v}O_2$):

$$CO = VO_2 / C_{a-v}O_2 \quad (9.26)$$

Cardiac output (CO) can be measured by the thermodilution technique, through Swan-Ganz catheter placed in the pulmonary artery, while $C_{a-v}O_2$ can be counted after blood samples' collection through pulmonary and peripheral artery. From Eq. (9.26), it appears that:

$$VO_2 = CO \times C_{a-v}O_2$$

or

$$VO_2 = CO \times Hb \times 1.34 \times 10 \times (S_{aO2} - S_{vO2}) \quad (9.27)$$

where S_{aO2} is the arterial blood oxygen saturation and S_{vO2} is the mixed venous blood oxygen saturation. Normal values of VO_2 are 225–275 ml/min or 110–160 ml/min/m^2. VO_2 estimation with Fick's technique has serious disadvantages, because it does not take into consideration the following aspects:

- Serious cardiac output's fluctuations exist.
- There is a 15% possibility of incorrect result in cardiac output measurement, using the thermodilution technique.
- Possibility of incorrect result in Hb concentration measurement, using heparinized blood samples, collected through catheters.

VO_2 measurement with indirect thermodilution technique is more accurate and less invasive. According to this method, VO_2 measurement is based on per minute inspired (V_I) and expired air volume (V_E) and mean O_2 and CO_2 concentration measurements in inspired (F_{IO2}, F_{ICO2}, respectively) and expired air (F_{EO2}, F_{ECO2}, respectively) [10]:

$$VO_2 = \left[(1 - F_{EO2} - F_{ECO2}) / (1 - Fi_{O2}) \right] \times F_{iO2} - F_{EO2} \times V_E \quad (9.28)$$

Under normal circumstances, VO_2 determines the oxygen delivery (DO_2) mainly through cardiac output's alterations. Inadequate oxygen delivery to cover tissue metabolic needs (for example, during hard exercise, anemia, hypoxemia, and shock) causes O_2 debt and tissue hypoxia. Oxygen extraction ratio (O_2ER) reflects in the VO_2/DO_2 ratio and represents the percentage of delivered O_2 that is consumed from tissues [10]:

$$O_2ER = VO_2 / DO_2$$

$$O_2ER = CO \times (C_{aO2} - C_{vO2}) \times 10 / CO \times C_{aO2} \times 10 \quad (9.29)$$

Normally, O_2ER values range between 0.2 and 0.3, meaning that only a quarter of delivered O_2 is used in aerobic metabolism, while the rest returns through venous circulation to the lungs. In cases of oxygen deprivation, the organism has the capacity to ensure adequate tissue oxygenation up to a point. For example, the fall in DO_2, caused by acute cardiac output reduction, is counterbalanced by an O_2ER rise, so that VO_2 remains stable. This O_2ER increase is caused by $C_{aO2} - C_{vO2}$ expansion (Eq. (9.29)) and is reflected in coincident S_{vO2} reduction, preventing O_2 debt and tissue hypoxia [9].

Mixed venous blood O_2 saturation (S_{vO2}) constitutes a tissue oxygenation index, while it expresses the relationship between average O_2 consumption and delivery to the whole body. In particular, according to Fick's Eq. (9.26), which measures cardiac output using O_2 consumption and arteriovenous O_2 difference:

$$CO = VO_2 / C_{a-v}O_2$$

$$CO = VO_2 / Hb \times 1.34 \times (S_{aO2} - S_{vO2}) \times 10$$

$$S_{vO2} = S_{aO2} - VO_2 / CO \times Hb \times 10 \quad (9.30)$$

Considering that during S_{vO2} measurement, arterial blood oxygenation and VO_2 are stable, S_{vO2} alterations reflect in cardiac output alterations. Continuous monitoring of S_{vO2} alterations, using special fiber-optic catheters in the pulmonary artery, constitutes a useful tissue oxygenation index in critically ill patients in intensive care units. However, some serious limitations exist:

– S_{vO2} has small sensitivity as a tissue oxygenation index, when microcirculation is disturbed, like upon sepsis, where perfusion allocation disturbance exists.
– S_{vO2} is usually increased upon hyperdynamic phase of septic shock despite tissue hypoxia, caused by inability of the tissues to use delivered O_2 [9].

9.2.7 Diffusion, Ventilation, and Perfusion Limitations

The resistance to gas flow through an airway is determined by several factors, including airway caliber and configuration, flow, physical properties of the gas, such as density and viscosity, and whether the gas flow is laminar or turbulent [11]. In acute respiratory failure that requires mechanical ventilation, the higher positive end-expiratory pressure (PEEP) reduces lung collapse and improves mechanics and gas exchange, while it also downregulated surfactant release and production and increased epithelial cell injury [12].

Acute respiratory distress syndrome (ARDS) is a well-known entity in critically ill patients, which usually appears with hypoxia, hypercapnia, and concomitantly increased work of breathing, due to increased dead space because of both surfactant dysfunction and lung inflammation [13, 14]. Clinical studies show a reduction in the work of breathing during ventilation with a mixture of oxygen and helium, with a concomitant gas exchange improvement [15]. Helium is an inert gas with a lower density than air, thus the flow of helium through an airway is less turbulent, leading to lower resistance, minimizing the necessary driving pressure to distribute oxygen to the alveoli, upgrading oxygenation [16], while it increases diffusion capacities of CO_2, resulting in gas exchange improvement [17]. Helium has also been used to reduce the work of breathing during exacerbations of asthma and COPD (chronic obstructive pulmonary disease) [17], without equivalent results, especially in intubated patients, because it decreases frictional resistance when the gas flow is turbulent but has no effect on the resistance to laminar flow [11].

Parameters related to macrocirculation, such as the mean arterial pressure, central venous pressure, cardiac output, mixed venous saturation, and central oxygen saturation, while being commonly used in the hemodynamic assessment and tissue perfusion in critically ill patients, have great limitations in shock, where microcirculation is disturbed [18, 19]. Numerous techniques have been developed for microcirculation assessment such as peripheral perfusion index and temperature gradient, for clinical assessment, laser Doppler flowmetry, tissue oxygen assessment electrodes, video microscopy (orthogonal polarization spectral imaging, sidestream dark field imaging, or incident dark field illumination), and near-infrared spectroscopy [20]. Recently, microvessel electrodes for tissue P_{O2} (P_{tO2}) measurement are used in indirect assessment, via P_{O2} levels, perfusion and/or regional oxygenation, especially in low-flow conditions. Actually, it is possible to measure continuously tissue oxygen partial pressure (P_{tO2}) and tissue carbon dioxide partial pressure (P_{tCO2}) noninvasively, using transcutaneous sensors. Carbon dioxide is approximately 20 times more diffusible than oxygen, and transcutaneous oxygen measurement is more sensitive to changes in perfusion than transcutaneous carbon dioxide measurement. In patients with normal lung function, increased F_{iO2} is associated with a parallel increase in P_{tO2} since, in patients with adequate blood flow, the P_{tO2} and P_{aO2} values are almost identical. A lack of increase in P_{tO2} after an increase in F_{iO2} suggests probable perfusion dysfunction and portends a worse outcome in septic shock patients [21, 22].

9.2.8 Pulmonary Gas Exchange Measurements

The measurement of pulmonary gas exchange has passed through many stages during the last 100 years [23]. Haldane and Priestley in 1935 reported that oxygen was actively secreted by the lung [24]. A few years later, the only way they had for detecting defective gas exchange was through patient's cyanoses. A breakthrough was the development of electrodes that could measure

P_{O2}, P_{CO2}, and pH in a sample of arterial blood [25, 26]. Consequently, clinicians could recognize the importance of ventilation-perfusion ratio disturbances and their role in hypoxemia and CO_2 retention during lung diseases [27]. The advent of digital computing has made a dramatic change in the understanding of pulmonary gas exchange.

The traditional way of measuring impaired gas exchange in patients with pulmonary disease has been blood gas analysis in arterial blood samples, while recently it seems beneficial to use a noninvasive method for measuring the pulmonary gas exchange . The patient breathes through a mouthpiece for 2 or 3 min until a state of gas exchange has been established, and the device enables the continuous measurement of inspired and expired P_{O2} and P_{CO2} using miniaturized sensors that can be taken to the bedside. A pulse oximeter is used to calculate the arterial P_{O2} using the oxygen dissociation curve while taking account of the effects of changes in P_{CO2} using the alveolar value. The difference between the end tidal P_{O2} and the calculated arterial P_{O2} is known as the oxygen deficit, which seems to be a very sensitive index of abnormal gas exchange [23, 28].

9.3 Conclusion Discussion

Gas molecules move down a pressure gradient. As a result, oxygen diffuses across the alveolar-capillary membrane from alveoli into the blood, while carbon dioxide diffuses in the opposite direction. Ventilation and perfusion matching is important in gas exchange, as ventilation must be sufficient to create a high partial pressure of oxygen in the alveoli. If ventilation is insufficient and the partial pressure of oxygen drops in the alveolar air, the capillary is constricted and blood flow is redirected to alveoli with sufficient ventilation. Arterial blood gas (ABG) analysis remains the traditional way of determining impaired gas exchange, while upon critical illness the monitoring and optimization of tissue perfusion by direct viewing and microcirculation management may become an achievable goal in the ideal resuscitation.

Key Major Recommendations

- Blood gas analysis and hemoximetry are recommended for evaluating a patient's ventilatory, acid-base, and/or oxygenation status (1A) [29].
- Blood gas analysis and hemoximetry are recommended for monitoring severity and progression of documented cardiopulmonary disease processes (1A) and are suggested for evaluating a patient's response to therapeutic interventions (2B) [29].
- Central venous blood gas analysis and hemoximetry are suggested to determine oxygen consumption in the setting of early goal-directed therapies (2B) [29].

References

1. Hughes JM. Assessing gas exchange. Chron Respir Dis. 2007;4(4):205–14.
2. Wagner P. The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. Eur Respir J. 2015;45:227–43.
3. Hsia CC, Hyde DM, Weibel ER. Lung Structure and the Intrinsic Challenges of Gas Exchange. Compr Physiol. 2016;6(2):827–95.
4. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. Eur Respir J. 2014;44(4):1023–41.
5. West JB, Wang DL, Prisk GK, et al. Noninvasive measurement of pulmonary gas exchange: comparison with data from arterial blood gases. Am J Physiol Lung Cell Mol Physiol. 2019;316(1):L114–8.
6. Filley GF, Macintosh DJ, Wright GW. Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. J Clin Invest. 1954;33:530–9.
7. Paulev P-E, Siggaard-Andersen O. Clinical application of the pO2-pCO2 diagram. Acta Anaesthesiol Scan. 2004;48(9):1105–14.
8. Golja P, Cettolo V, Francescato MP. Calculation algorithms for breath-by-breath alveolar gas exchange: the unknowns. Eur L Appl Physiol. 2018;118(9):1869–76.
9. Wolff CB. Oxygen delivery: the principal role of the circulation. Adv Exp Med Biol. 2013;789:37–42.
10. Soni N, Fawcett WJ, Halliday FC. Beyond the lung: oxygen delivery and tissue oxygenation. Anaesthesia. 1993;48(8):704–11.
11. Leatherman J, Romero R, Shapiro R. Lack of benefit of Heliox during mechanical ventilation of subjects with severe air-flow obstruction. Respir Care. 2018;63(4):375–9.
12. Thammanomai A, Hamakawa H, Bartolák-Suki E, et al. Combined effects of ventilation mode and

positive end-expiratory pressure on mechanics, gas exchange and the epithelium in mice with acute lung injury. PLoS One. 2013;8(1):e53934.
13. Bercker S, Busch T, Donaubauer B, et al. Mechanical ventilation and fluid management in acute lung injury. Effects on gas exchange and hemodynamics. Anaesthesist. 2009;58(4):410–4.
14. Yilmaz S, Daglioglu K, Yildizdas D, et al. The effectiveness of heliox in acute respiratory distress syndrome. Ann Thorac Med. 2013;8(1):46–52.
15. Beurskens C, Wösten-van Asperen R, Preckel B, et al. The potential of heliox as a therapy for acute respiratory distress syndrome in adults and children: a descriptive review. Respiration. 2015;89(2):166–74.
16. Gentile M. Inhaled medical gases: more to breathe than oxygen. Respir Care. 2011;56(9):1341–57. discussion 1357–9
17. Beurskens C, Brevoord D, Lagrand W, et al. Heliox improves carbon dioxide removal during lung protective mechanical ventilation. Crit Care Res Pract. 2014;2014:954814.
18. De Backer D, Hollenberg S, Boerma C, et al. How to evaluate the microcirculation: report of a round table conference. Crit Care. 2007;11(5):R101.
19. Molnar Z, Nemeth M. Monitoring of tissue oxygenation: an everyday clinical challenge. Front Med (Lausanne). 2018;4:247.
20. Tafner PFDA, Chen FK, Filho RR, et al. Recent advances in bedside microcirculation assessment in critically ill patients. Rev Bras Ter Intensiva. 2017;29(2):238–47.
21. Boerma EC, Mathura KR, van der Voort PH, et al. Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Crit Care. 2005;9(6):R601–6.
22. Lima A. Current status of tissue monitoring in the management of shock. Curr Opin Crit Care. 2016;22(3):274–8.
23. West BJ. A lifetime of pulmonary gas exchange. Physiol Rep. 2018;6(20):e13903.
24. Haldane JS, Priestley JG. Respiration. London: Oxford University Press; 1935.
25. Millikan GA. The oximeter, an instrument for continuously the oxygen saturation of arterial blood in man. Rev. Sci. Instrumentalist. 1942;13:434–44.
26. Severinghaus JW, Honda Y. History of blood gas analysis VII. Pulse oximetry. J Clin Monit. 1987;3:135–8.
27. Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J Appl Physiol. 1949;1:825–47.
28. West JB, Wang DL, Prisk GK. Measurements of pulmonary gas exchange efficiency using expired gas and oximetry: results in normal subjects. Am J Physiol Lung Cell Mol Physiol. 2018;314(4):L686–9.
29. Davis MD, Walsh BK, Sittig SE, et al. AARC clinical practice guideline: blood gas analysis and hemoximetry: 2013. Respir Care. 2013;58(10):1694–703.

Biomarkers and Pulmonary Function Test

10

Ruslan Abdullayev and Seniyye Ulgen Zengin

Abstract

A biomarker is an objectively measured characteristic that indicates normal or pathological state. Biomarkers of pulmonary function are clinical signs, radiological findings, or laboratory findings that reflect lung functions. In this chapter, we have classified biological markers of pulmonary functions in seven groups as clinical markers, lung volume and pressure markers, radiological markers, lung tissue, blood, sputum, and exhaled breath markers.

Keywords

Pulmonary function test · Respiratory function test · Markers · Biomarkers

Abbreviations

BMI	Body mass index
$C_{alv}NO$	Alveolar nitric oxide
CC-16	Club cell protein 16
CCL18	CC chemokine ligand 18
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computerized tomography
DLCO	Diffusing capacity for carbon monoxide
DNA	Deoxyribonucleic acid
EBC	Exhaled breath condensate
EGFR	Epidermal growth factor receptor
$FEF_{25–75}$	Forced expiratory flow at 25–75% of lung volume
FeNO	Fractional excretion of nitric oxide
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GSH-Px	Glutathione peroxidase
GST	Glutathione-S-transferase
He	Helium
HNP	Human neutrophil peptide
ICAM-1	Intracellular adhesion molecule-1
ICAM-2	Intracellular adhesion molecule-2
IGFBP-2	Insulin-like growth factor-binding protein 2
IL-8	Interleukin-8
IPF	Idiopathic pulmonary fibrosis
KL-6	Krebs von den Lungen-6
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
MMP	Matrix metalloproteinase
NE	Neutrophil elastase
$PaCO_2$	Arterial blood partial pressure of carbon dioxide
PaO_2	Arterial blood partial pressure of oxygen
PFT	Pulmonary function test

R. Abdullayev (✉) · S. U. Zengin
Department of Anesthesiology and Reanimation, Marmara University School of Medicine, Istanbul, Turkey

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_10

PON1	Paraoxonase 1
ROS	Reactive oxygen species
RV	Residual volume
SOD	Superoxide dismutase
SP-A	Surfactant protein A
SP-D	Surfactant protein D
sRAGE	Soluble receptor for advanced glycation end products
TLC	Total lung capacity
TNF-α	Tumor necrosis factor-α
TOS	Total oxidative status
VEGF	Vascular endothelial growth factor
VOCs	Volatile organic compounds

10.1 Introduction

In 2001, US National Institute of Health working group recommended a standardized definition for biomarkers, which was defined as "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [1]. Most individuals understand biomarkers as a laboratory-based test that provides an objective and reproducible information about the disease state. However, according to the definition, physiologic parameters (e.g., FEV_1, FVC, $FEF_{25–75}$) and bioimaging features (e.g., low-density areas and emphysematous holes on CT scan) could qualify as biomarkers. Biomarkers should enable tailoring of treatment interventions for the patients that will maximize therapeutic benefits and minimize the risk of treatment. Biomarkers must be safe, accurate, inexpensive, and easily measurable; and the results must be reproducible across sex, age, and different racial backgrounds. Ideal biomarker should enable clinician to better manage the disease state, typically meaning, intervention with more effective therapies for those who need them and elimination of ineffective or even harmful therapies for those who will not benefit. Ideal biomarker should be (1) superior (the test should surpass in performance current standards), (2) actionable (the test should change patient management), (3) valuable (the test should improve patient outcomes), (4) economical (the implementation of the biomarker should be cost-effective), and (5) clinically deployable (there should be a pathway for the biomarker to be implemented in a clinical laboratory) [2].

10.2 Discussion and Analysis of Main Topic

10.2.1 Clinical Markers

Symptoms, signs, and physical examination findings are traditional and indispensable markers of pulmonary functions and disease severity. Despite being subjective, *symptoms* are included in many outcomes, indicating disease progression, response to treatment, and impact on individual health status. Many tests based on symptoms are applied. A questionnaire named Chronic Obstructive Pulmonary Disease (COPD) Assessment Test is one of them. Degree of breathlessness, exercise limitation, and low body mass index (BMI) are examples of the *signs* of pulmonary function. They characterize the health status and are associated with disease progression, morbidity, and mortality. *Composite scores* have been introduced into clinical practice to overcome the problems associated with using only one parameter, either sign or symptom. BODE index (Body mass index, airflow Obstruction, Dyspnea, and Exercise), mBODE (BODE modified in grading of walked distance), ADO (Age, Dyspnea, airflow Obstruction), DOSE (Dyspnea, Obstruction, Smoking, Exacerbation) are some examples for composite scores. They have been introduced to characterize disease activity, severity, impact on health status, and prognosis.

10.2.2 Lung Volume-Pressure Markers

10.2.2.1 Spirometry

Spirometry, the traditional pulmonary function test (PFT), is the most basic and useful test for assessing the lung functions. It includes the

measurement of air that enters in or exits from the lungs during forced respiration. The most commonly measured markers are forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and FEV_1/FVC ratio. The *FVC* is the amount of air that can be forcefully exhaled beginning from the total lung capacity to the residual volume. The *FEV_1* is the amount of air that is expelled at the first second of FEV maneuver. The *FEV_1/FVC* ratio is another marker and indicates the airway obstruction. These markers are important for guiding in the diagnosis of obstructive and restrictive pulmonary diseases. FEV_1/FVC ratio is decreased in obstructive patterns, whereas it is normal in restrictive diseases. FEV_1/FVC ratio below the fifth percentile of normal predicted value or one below 0.7 (70%) is considered to be abnormal and indicates an obstructive pattern. Forced expiratory flow at 25–75% of lung volume (*$FEF_{25–75}$*) had been developed as an indicator of small airway disease; however, being nonspecific, this marker is no longer recommended for interpretation. Some laboratories include maximum voluntary ventilation (*MVV*), the patient's ability to breathe in and out as rapidly and deeply as possible, as part of routine spirometry. A normal value is about 40 times normal FEV_1, and values under 30 times normal are considered low. If the test properly performed, this marker is indicative of upper airway obstruction or neuromuscular weakness [3].

10.2.2.2 Lung Volumes

Although being valuable in differentiating obstructive and restrictive patterns, spirometry does not provide information about the values in which residual volume (RV) is used. Lung volume measurements are needed to have information about RV, FVC, and total lung capacity (TLC). Body plethysmography, helium dilution, and nitrogen washout are methods for measuring the lung volumes. Lung volume measurement is especially important in restrictive patterns, where reduced *FVC* is a good marker. In obstructive disorders, lung volume measurements provide valuable information as well; *RV* and *RV/TLC* ratio are being markers of airway trapping and *TLC* is a marker of hyperinflation [3]. Figure 10.1 demonstrates different portions of lung volumes and capacities.

10.2.2.3 Maximal Respiratory Pressures

Maximal inspiratory pressure (*MIP*) is the maximal pressure that can be produced by the patient trying to inhale through a blocked mouthpiece. Maximal expiratory pressure (*MEP*) is the maximal pressure measured during forced expiration through a blocked mouthpiece after a full inhalation to TLC. These markers can provide valuable information about airway obstruction and muscle weakness [3].

10.2.2.4 Diffusing Capacity for Carbon Monoxide

Diffusing capacity of lung for carbon monoxide (*DLCO*) is a measure of gas exchange. The patient inhales air with trace amounts of carbon monoxide (CO) and helium (He) from RV to TLC, holds for 10 s, and then quickly exhales. The change in CO and He concentrations is measured. The DLCO is decreased in diseases with reductions in lung volume, pulmonary parenchymal diseases, or pulmonary vascular disorders. It is increased in disorders like asthma, obesity, and alveolar hemorrhage [3].

10.2.3 Image Markers

Quantitative computerized tomography (CT) and CT densitometry are specific modification methods of high-resolution CT with software incorporation, which are able to objectively measure the severity of emphysema. They correlate well with spirometric measurements, and the literature data suggest that the indices can even predate the spirometric changes in many instances [4]. Some of these indices are *airway wall thickness*, *emphysema*, and *bronchiectasis*. These indices are frequently studied as to have correlation with the disease severity, exacerbations, and prediction of mortality. Airway wall thickness and emphysema, measured quantitatively by CT, had correlation with decreased lung functions.

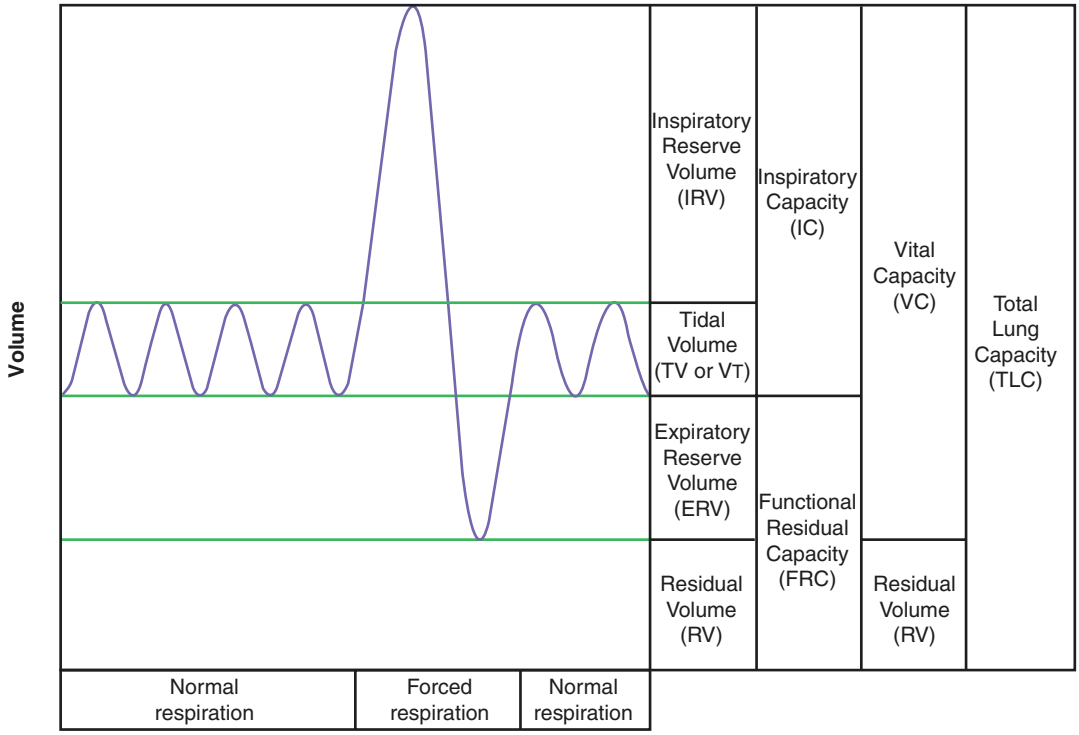

Fig. 10.1 Lung volumes and capacities

10.2.4 Lung Tissue Markers

10.2.4.1 Gene Expression Markers

Gene expression markers provide another insight into biomarker research. Many genes have been reported to be differentially expressed in emphysema and COPD. Genes that are responsible for tissue destruction have been found to be increased in emphysematous lung tissue, and they were correlated with decreased FEV_1. Gene expression profiles of the lung tissue samples from the patients with COPD correlated with $FEF_{25–75}$. Genes responsible for apoptosis, extracellular matrix synthesis, and degradation were upregulated, while anti-inflammatory genes were downregulated [5].

10.2.4.2 Protein Markers

Protein markers of the lung tissue are another perspective. Many theories regarding the protease/antiprotease hypothesis in pulmonary diseases implicate the idea to look for biomarkers that assess protease activities and their degradation products as well. However, this approach never comes to reality. *Elastase* is very difficult to measure, as it is rapidly inhibited by local antiproteases. So are the degradation products of elastin, as they are not lung specific. Bronchoalveolar lavage has been used to overcome these problems, but drawbacks like invasiveness of the procedure and lack of standardization have been obstacles in the biomarker research. *Neutrophil elastase* detection is an alternative way of measuring elastase activity in the lung. The cleavage of the surrounding structures is a biochemical proof of the enzyme activity. A specific product of *fibrinogen* named *Aα-Val360* has been used as a biomarker, and the values were shown to be correlated with spirometric indices. Neutrophil elastases play a major role in activating other proteolytic enzymes, such as cathepsin B, matrix metalloproteinases (MMPs), and tumor necrosis factor (TNF)-α. Serum levels of *collagen type I* and *type VI frag-*

ments, the degradation products of collagen by MMPs, were also correlated with spirometric indices, disease severity, and mortality.

10.2.5 Blood Markers

10.2.5.1 Inflammatory Markers

Reduced levels of vitamin D have been shown to be correlated with FEV_1. Low levels of club (Clara) cell protein 16 (CC-16) were correlated with FEV_1 decline. Proteins of epidermal growth factor receptor (EGFR) signaling pathway were correlated with FEV_1 changes. Many biomarkers were studied in COPDGene and ECLIPSE studies, and *CC-16*, *fibrinogen*, soluble receptor for advanced glycation end products (*sRAGE*), C-reactive protein (*CRP*), and surfactant protein D (*SP-D*) were demonstrated to be associated with airflow limitation and FEV_1 decline. Bradford et al. have used cytokine and chemokine panels from the COPDGene and SPIROMICS studies, and they have demonstrated that *eotaxin* and *IL-6* were correlated with airflow obstruction [6]. In a study by Mendy et al., patients with high CRP, *eosinophil count* <2%, hypo*albumin*emia, and hypo*vitamin*osis *D* had low baseline FEV_1 values [7]. Many serum inflammatory markers have been investigated with regard to their association with disease progression, exacerbations, prognosis, and mortality [5]. As mentioned earlier, only few of them have been shown to be significantly associated with pulmonary functions, but future studies in this respect may reveal more data about the association of these markers and pulmonary functions. These markers may be used as good surrogates of currently used pulmonary function tests.

YKL-40, one of the members of mammalian chitinase-like protein family, is another marker. It is thought to be involved in pathophysiological processes, such as cell growth, migration, chemotaxis, reorganization, and tissue remodeling. It may play an important role in inflammation and remodeling in COPD. YKL-40 is produced by macrophages, neutrophils, monocytes, airway epithelium, and vascular smooth muscles and may serve as a biomarker of lung functions, disease progression, and exacerbations. Elevated levels of serum YKL-40 have been found to be negatively correlated with FEV_1%predicted. No correlation was observed with FEV_1, but taking into consideration the scarcity of material in the current literature, future studies in this respect would reveal more data, including the association of lung functions with sputum levels of the marker [8].

Eosinophils are another example of inflammatory cells that under certain conditions recruited to the lungs where they facilitate inflammatory reaction through the secretion of cytokines, chemokines, and cytotoxic granular products. High levels of eosinophils have been found in blood, sputum, bronchoalveolar lavage fluid, and bronchial tissue in the patients with COPD and asthma. *Absolute* or *relative cell count of* circulating *eosinophils* can be used as marker, but many studies have used 2% for relative number of the cells as reference; and values above this showed accelerated decline in FEV_1, and better response to corticosteroids [9].

10.2.5.2 Oxidative Stress Biomarkers

In human body, there is a balance between toxicity of oxidants and protective functions of antioxidant defense systems. Increased oxidative burden plays an important role in the pathogenesis of many pulmonary diseases, and this oxidant/antioxidant balance is critically important in the maintenance of pulmonary functions. Several biomarkers of oxidative stress are available, including reactive oxygen species (ROS) themselves (i.e., *superoxide anion*, *hydroxyl radical*, and *hydrogen peroxide*). ROSs are generally too reactive with short half-lives, so it is difficult to measure them. Taking this into consideration, it is more suitable to estimate oxidative stress by measuring the oxidation target products and various antioxidants.

Lipid peroxidation products are the major products of oxidative damage. They mainly include *malondialdehyde* and to a lesser extent *lipid peroxides*, *conjugated dienes*, *oxidized-LDL*, and *8-isoprostane*. There are also protein oxidation products, such as *protein carbonyls* and *advanced protein oxidation products*.

Instead of measuring different oxidant species separately, total oxidative status (*TOS*) in plasma can be measured. TOS measurement is performed based on the principle of the oxidation of ferrous ion to ferric ion by the oxidants, which is measured spectrophotometrically. *Oxidatively damaged DNA* is another marker of oxidative damage and is measured by single-cell gel electrophoresis (also known as comet assay). A significant increase in DNA damage has been demonstrated in COPD patients.

Thiols are organic compounds that contain a sulfhydryl group (–SH). There are intracellular thiols, maintaining highly reduced environment inside the cell, and extracellular thiols as well. A significant decrease of *protein SH groups* have been observed in COPD patients, compared with normal population. Some authors have demonstrated an association between the biomarker decrease and the disease severity. Regarding *non-protein SH groups*, studies have demonstrated conflicting results in association of the biomarker and disease severity, both progression of the disease and no difference.

There is scarcity of data about the certain association between antioxidants and pulmonary functions. Most studies in the literature focus on the association between various antioxidant levels, measured by many different tests, and pulmonary disease severity, exacerbations, progression, response to treatment, and mortality. Studies focusing on the direct measurement of the above-mentioned biomarkers together with spirometric pulmonary function tests in homogenous groups would give valuable data about the possibility of the future use of these markers as surrogates of the currently used tests.

Plasma levels of many antioxidant nutrients, such as *vitamin A*, *C*, *E*, and *α*- and *β-carotenes*; essential trace elements, such as *selenium (Se)*, *zinc (Zn)*, *iron (Fe)*, *copper (Cu)*, *rubidium (Rb)*; and *uric acid* have been investigated with regard to their association with pulmonary disease severity, progression, and exacerbations. However, conflicting results have been demonstrated, and there are still few data about the direct association between these and PFTs.

Enzymatic antioxidant activity can be measured in the blood. Enzymes, such as superoxide dismutase (*SOD*), *catalase*, and glutathione peroxidase (*GSH-Px*), and to a lesser extent, glutathione-S-transferase (*GST*), paraoxonase 1 (*PON1*), and *ceruloplasmin ferroxidase* have been studied in this regard in COPD patients. Again, there are many studies in the literature focusing on the association between these enzyme activities and pulmonary disease severity, exacerbations, progression, response to treatment, and mortality. There is scarcity of data about the certain association between these enzyme activities and PFTs [10].

10.2.5.3 Biomarkers of Idiopathic Pulmonary Fibrosis (IPF)

Biomarkers of IPF can be classified as alveolar epithelial markers, fibrogenesis and extracellular remodeling markers, chemokines, growth factors and adhesion molecules, and circulating cells.

Alveolar epithelial markers are associated with alveolar epithelial cell damage. These are Krebs von den Lungen-6 (*KL-6*) *antigen* and surfactant protein A and D (*SP-A*, *SP-D*). Fibrogenesis and extracellular remodeling markers are matrix metalloproteinases (*MMP-1*, *MMP-7*), lysyl oxidase-like 2 (*LOXL2*), and *periostin*. Correlation between higher MMP-7 and lung functions (FVC, DLCO) has been demonstrated. Chemokines are CC chemokine ligand 18 (CCL18) and interleukin-8 (*IL-8*). *CCL18*, a small protein derived from alveolar macrophages, has been demonstrated to be negatively correlated with TLC and DLCO. *IL-8*, a cytokine, has been demonstrated to be negatively correlated with TLC, DLCO, and VC. Growth factors and adhesion molecules are *YKL-40*, insulin-like growth factor-binding protein 2 (*IGFBP-2*), intracellular adhesion molecule-1 and -2 (*ICAM-1* and *ICAM-2*), and vascular endothelial growth factor (*VEGF*). An association between these markers and some spirometric indices like DLCO or VC has been demonstrated in studies, but further longitudinal studies are necessary to evaluate their usefulness as biomarkers.

Examples for circulating cells are *Sema7a⁺ T cells* and *fibrocytes*, but there are limited data about these markers in the literature [11].

10.2.5.4 Arterial Blood Gases

Blood gas measurement can provide valuable information about the pulmonary function. The two measured variables, PaO_2 (arterial blood partial pressure of oxygen) and $PaCO_2$ (arterial blood partial pressure of carbon dioxide), are good markers of various pathophysiological states. Low *PaO_2* (i.e., values below 60 mm Hg or 8 kPa) indicates decreased pulmonary function, provided there are normal atmospheric conditions. Normal range for $PaCO_2$ is 35–45 mm Hg or 4.7–6 kPa, and it is an indicator of CO_2 production and elimination. *$PaCO_2$* is a good marker of pulmonary function, provided there is no hypermetabolism. Higher values indicate hypoventilation and are suggestive of many disorders of obstructive and restrictive pattern. Lower values indicate hyperventilation, either physiological or pathological.

10.2.5.5 Telomeres and Sirtuins

Telomeres and sirtuins are related with lung aging in COPD patients. *Telomeres*, composed of repetitive sequences of nucleic acids, are protective structures that stabilize chromosome ends. Telomere repeats shorten during cell division. COPD patients have shorter telomeres on their peripheral blood leukocytes, and association between the disease and telomere length was described. A correlation of telomere length with FEV_1 and FEV_1/FVC ratio was also demonstrated [5].

Sirtuins are enzymes that belong to silent information regulatory family and are responsible for gene silencing. Sirtuins have anti-inflammatory and anti-aging properties. Their levels in peripheral blood mononuclear cells are decreased in COPD patients. Sirtuin levels have been demonstrated to be positively correlated with FEV_1 and diffusion capacity [5].

10.2.6 Sputum Biomarkers

Sputum is considered a noninvasive method for biomarker sampling. The drawbacks of the methods are that it highly varies in stable disease and its exacerbations, and it contains many oral cavity cells and nonviable cells as well. Moreover, the patient must produce sputum to be sampled, and this is not always the case. Many sputum biomarkers have been studied with regard to their association with pulmonary disease progression, exacerbations, prognosis, and mortality. [4] ECLIPSE study revealed valuable data about the association of sputum biomarkers and pulmonary functions. Increased *neutrophil count* was associated with lung functions. High neutrophil elastase (*NE*), human neutrophil peptides (*HNP*s), *IL-8*, and *MMP-9* in spontaneous sputum are associated with FEV_1 decline in COPD patients.

10.2.7 Exhaled Breath Biomarkers

10.2.7.1 Volatile Organic Compounds (VOCs)

Analysis of exhaled breath helps in the discrimination of many pulmonary diseases. One of the examples is the discrimination of the COPD profile with either higher sputum eosinophilia or neutrophilia. Sputum cell count correlates well with exhaled breath compounds. However, methodological issues of VOC testing should be overcome before routine application of these tests as surrogates of pulmonary functions [5]. *P-cymene* had negative correlation with FVC, VC, and DLCO. *Ethylbenzene* had negative correlation with diffusion capacity per liter lung volume (%DLCO/VA) [12].

10.2.7.2 Exhaled Breath Condensate (EBC)

Collection of cooled exhaled breath condensate is another good way of sampling the airway lining fluid, given its noninvasive nature. For example, EBC acidification is a reflection of airway

acidification, and this can serve as a surrogate of lung function and disease severity. Again, H_2O_2 is a marker of oxidative stress, and it correlates well with COPD severity and exacerbations. Fractional excretion of nitric oxide (*FeNO*) is another measured parameter, and it serves in aiding the diagnosis of COPD phenotypes, as its higher values (i.e., FeNO >32 ppb) correlate with sputum eosinophilic percentage. A negative correlation was demonstrated between H_2O_2 and *8-isoprostane* with DLCO %predicted. Alveolar nitric oxide $C_{alv}NO$ was found to be higher in the patients with declining lung functions [12]. Notwithstanding, validation of assays and interpretation of clinical impact need to be solved before these measurements become a part of the routine practice [5].

10.3 Conclusion

There are many types of biological markers that reflect lung functions. These markers can be measured in invasive and noninvasive manner. There are plenty of data in the literature about these markers. However, most have investigated the relationship of the parameters with the disease severity, progression, exacerbations, responses to treatment, and mortality. The literature data still lack the exact association of imaging, blood, sputum, and breath markers with traditional pulmonary function tests measured by spirometry.

Key Major Recommendations

This chapter includes the biological markers of human body that could be used as good surrogates of pulmonary functions. Advantages and disadvantages of the described methods, including invasiveness and cost, must be weighted before deciding which test to perform. Taking into account the scarcity of data in the literature regarding the exact association of many biomarkers with conventional pulmonary function tests, the clinicians must always use these biomarkers together with traditional assessments of lung functions, such as symptoms, physical signs, spirometric measurements, and blood gases.

References

1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
2. Hollander Z, DeMarco ML, Sadatsafavi M, et al. Biomarker development in COPD. Moving from P values to products to impact patient care. Chest. 2017;151:455–67.
3. Dempsey T, Scanlon PD. Pulmonary function tests for the generalist: a brief review. Mayo Clin Proc. 2018;93:763–71.
4. Crossley D, Renton M, Khan M, et al. CT densitometry in emphysema: a systematic review of its clinical utility. Int J Chron Obstruct Pulmon Dis. 2018;13:547–63.
5. Cherneva RV, Kostadinov DT. Biomarkers in COPD – challenging, real or illusive. Folia Med. 2018;60:351–63.
6. Bradford E, Jacobson S, Varasteh J, et al. The value of blood cytokines and chemokines in assessing COPD. Respir Res. 2017;18:180–9.
7. Mendy A, Forno E, Niyonsenga T, et al. Blood biomarkers as predictors of long-term mortality in COPD. Clin Respir J 2018;12:1891–1899.
8. Tong X, Wang D, Liu S, et al. The YKL-40 protein is a potential biomarker for COPD: a meta-analysis and systematic review. Int J Chron Obstruct Pulmon Dis. 2018;13:409–18.
9. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? Lancet Respir Med. 2017;5:747–59.
10. Zinellu E, Zinellu A, Fois AG, et al. Circulating biomarkers of oxidative stress in chronic obstructive pulmonary disease: a systematic review. Respir Res. 2016;17:150.
11. Guiot J, Moermans C, Henket M, et al. Blood biomarkers in idiopathic pulmonary fibrosis. Lung. 2017;195:273–80.
12. Hayton C, Terrington D, Wilson AM, et al. Breath biomarkers in idiopathic pulmonary fibrosis: a systematic review. Respir Res. 2019;20:7.

Part III

Are There Any Specific Clinical Noninvasive Ventilation Indications and Pulmonary Function Measurement?

11 Dyspnea During Noninvasive Ventilation Implications for Respiratory Function

M. I. Matias, C. Cortesão, P. S. Santos, and Antonio M. Esquinas

Abstract

Dyspnea is a common and disturbing symptom that hosts multiple subjective experiences, and therefore, it is very hard to classify. Although noninvasive ventilation (NIV) can reduce it, respiratory discomfort can persist, reappear, or increase after NIV, and it can be multifactorial. Dyspnea during NIV is prevalent and is associated with worse prognosis.

Keywords

Dyspnea · Noninvasive ventilation · Respiratory function · NIV settings · NIV complications

Abbreviations

COPD	Chronic obstructive pulmonary disease
NIV	Noninvasive ventilation

M. I. Matias (✉) · C. Cortesão · P. S. Santos
Pulmonology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

11.1 Introduction

Dyspnea is a common and disturbing symptom that hosts multiple subjective experiences, and therefore, it is very hard to classify [1]. However, regarding quality of dyspnea, there are three types that are currently considered, and about quantifying dyspnea, there are multiple questionnaires and scales. In addition, in the case of cognitive impairment, heteroevaluation scales have also been validated [2].

Although noninvasive ventilation (NIV) can reduce dyspnea due to respiratory muscle unloading, respiratory discomfort can persist, reappear, or increase after NIV. Evaluation of a patient with dyspnea always starts with a history and physical examination, and in the context of fast deterioration, the ABCDE approach should be conducted [3–5].

Dyspnea, in mechanically ventilated patients, can be multifactorial, and therefore, contributions from several factors should be taken into consideration starting with the underlying disease and its stage, comorbidities, and mental status, but also ventilator settings and interface, as well as the possibility of complications, some of which arise acutely and can be life-threatening [3, 5].

Dyspnea during NIV should be taken into high consideration since it is prevalent and is associated with NIV failure and increased risk of intubation and higher short-term and long-term mortality [5].

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_11

11.2 Discussion and Analysis of the Main Topic

11.2.1 Definition and Physiopathology of Dyspnea

Dyspnea is a common and disturbing symptom consensually defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity." It is an internal state of respiratory discomfort consisting of a set of distinct sensations resulting from the interaction of physiological, social, and environmental factors that generate a unique physiological and behavioral response [1].

Physiopathology of dyspnea depends on excitatory and inhibitory information as well as motor perceptions. These sensory-motor mechanisms give rise to sensations related to breathing, and they originate from chemoreceptors as well as receptors in the airways, lung parenchyma, and respiratory muscles. They assess multiple stimuli as changes in the blood gases and pH level, as well as mechanical status of the respiratory system, producing afferent impulses to the brain stem witch elaborates a suitable response [4].

Breathing is automatic while the load remains constant, or when load changes are anticipated unconsciously, the ventilatory drive in the brain stem (enhanced by stimuli like hypercapnia, hypoxia, hyperthermia, or exercise) is accompanied by a suitable return in the stretch receptor. However, if unexpected changes are produced, that is, the motor drive to breathe (i.e., corollary discharge) is not matched by afferent feedback from mechanoreceptors in the lungs, airways, and chest wall, then cerebral cortex is activated. This means breathing becomes a conscious act, and one becomes aware that if the result of the effort no longer corresponds to the demands, then this is perceived as uncomfortable [4].

Sensory afferent stimulus and corresponding triggered mechanisms are summarized in Table 11.1.

Table 11.1 Sensory afferent stimulus and corresponding triggered mechanisms

Mechanism	Stimulus
Chemoreceptors	Hypoxemia, hypocapnia, acidosis
Mechanoreceptors	Hyperinflation, alveolar collapse, muscle distension
J receptors	Pulmonary vascular congestion
Airway C fibers	Inhalation of irritating products
Metabolic receptor	Metabolic activity of the ventilatory pump

11.2.2 Measurements and Assessment

Dyspnea hosts multiple subjective experiences; however, the wide range of afferent information described earlier (Table 11.1) may be associated more specifically to a particular dyspnea description.

With regard to the *quality of dyspnea*, the following types are currently considered and best characterized [6–8]:

- *Work or effort in breathing* (perception of excessive breathing force/effort):
  - Can occur in situations of high minute ventilation, situations of increased impedance to inspiration (e.g., at high lung volumes in a hyperinflated lung with increased lung elastance), and situations placing inspiratory muscles at a disadvantageous length or even weakness of this muscles. This feeling may occur even when gas exchange needs are ensured. It is highly associated with obstructive diseases of the airways and diseases that deteriorate respiratory mechanism or decrease the performance of the respiratory muscles like neuromuscular disorders [6–9].
- *Chest tightness* (sense of thoracic restriction):
  - It is a sensation relatively specific from stimulation of airway receptors associated with episodes of bronchoconstriction occurring namely in obstructive lung diseases [6–9].
- *Air hunger/unsatisfied inspiration* (unsatisfied urge to breathe):
  - It occurs in states where ventilatory demand exceeds the capacity to provide it. Appears

to originate from a "corollary discharge," an imbalance between an increased motor drive to breathe (efferent motor command) that was not matched by an inhibitory afferent feedback from mechanoreceptors in the respiratory system. "Air Hunger" is not specific of any disease or stimulus, it may occur in conditions characterized by restrictive mechanics and situations of limited tidal volume, for example, in dynamic hyperinflation. Can be enhanced by stimuli that increase ventilatory drive (hypoxia, hypercapnia, acidosis…) and may be relieved by a positive feedback from mechanoreceptors, providing information about achieved pulmonary ventilation [6–9].

Patients under noninvasive ventilation generally experience mixed respiratory sensations. Increased ventilatory drive (hypoxia, hypercapnia, acidosis, hyperthermia…) occurs in patients with a low functional reserve, for example, with weakened respiratory muscles, bronchospasm, or hyperinflated lungs with increased impedance to inspiration and generating inadequate tidal volume, and many other different constraints generate mixed qualities of dyspnea [6–9].

On the other hand, for *quantifying dyspnea,* several measuring instruments are proposed:

- *Direct approach:* patients who are able to answer simple questions (guided questioning and rating scales):
  - Intensity: Borg scale, visual analog scale (VAS), or modified Medical Research Council (mMRC) scale [2, 6–8].
  - Multidimensionality: baseline index of dyspnea (BDI), transitional index of dyspnea.
  - Specific pathology: for example, New York Heart Association scale [2, 6–8].
- *Indirect approach*: clinical surrogates:
  - Heteroevaluation scales: cognitive impairment may interfere with dyspnea self-report. Respiratory Distress Observation Scale (RDOS) is based on observable signs and is validated in noncommunicative patients [2].
  - Biomarkers: the electromyographic activity of the extradiaphragmatic inspiratory muscles and the premotor inspiratory potentials detected on the electroencephalogram, which are validated instruments [7].

11.2.3 Dyspnea Approach in Noninvasive Ventilated Patient

NIV can reduce dyspnea due to respiratory muscle unloading; however, dyspnea can persist, reappear, or increase after NIV.

Although patient's words may help indicating the underlying mechanisms, as seen earlier, the subjectivity of dyspnea hinders the determination of the diagnosis and severity of the underlying condition. Evaluation of a patient with dyspnea always starts with a history and physical examination. It is important to determine acute versus chronic dyspnea, intermittent versus persistent, and aggravating factors like effort, emotional stress, and body position, and in the context of rapid deterioration, the ABCDE approach should be conducted [3].

In addition to a detailed and necessary semiology, laboratory, imagiological, and clinical studies may have diagnostic utility to confirm the formulated hypotheses.

Dyspnea, in mechanically ventilated patients, can be multifactorial, and therefore, contributions from several factors should be considered starting with the underlying disease and its stage, patient's comorbidities, but also ventilator settings and interface, as well as the possibility of complications, some of which arise acutely and can be life-threatening [3, 6–8].

- *Dyspnea causes arising from the respiratory system* [3, 7].
  - *Underlying disease:* In the presence of preexisting underlying comorbilities, namely respiratory or cardiac, any increase in the work of breathing or worsening of ventilation-perfusion relationships and consequently pH and blood gas alterations may precipitate and perpetuate dyspnea if not resolved.

- *Pneumothorax* may occur particularly in the presence of emphysema and elevated EPAP or unusually large tidal volumes are used.
- *Pleural effusion* is a common complication among others of pulmonary infection or cardiac decompensation, which can reduce compliance and worsen ventilation-perfusion relations.
- *Atelectasis:* alveolar collapse and decreased tidal volume can lead to dyspnea.
- *Acute respiratory distress syndrome (ARDS):* many situations can lead to ARDS and worsen the ventilation-perfusion ratio causing dyspnea.
- *Respiratory infection*: present in the beginning or complicating the course. Can cause increased secretions, precipitation of bronchospasm, increased compliance and work of breathing. There is also an increase of death space, which worsens ventilation-perfusion relationship.

• *Dyspnea due to patient-ventilator characteristics.*

Inappropriate ventilator settings: optimizing inappropriate ventilator settings could reduce dyspnea intensity in 35% of patients during NIV [4]:

- *Patient-ventilator asynchrony*: due to inadequate definition of inspiratory and expiratory trigger and inspiration and expiration times [6, 7].
- *Low inspiratory flow*: associated with the sense of higher inspiratory muscle effort and on the other hand, increasing inspiratory flow originates respiratory muscle relaxation [6, 7].
- *Low pressure support levels*: associated with a sense of excessive inspiratory effort [6, 7].
- *Low tidal volumes*: in the case of increased ventilatory drive, via "corollary discharge," a low tidal volume may not produce an inhibitory afferent feedback from mechanoreceptors, causing "air hunger "[6, 7].
- *Intrinsic positive end-expiratory pressure (PEEP),* for example, in the case of bronchospasm, increase impedance to inspiration can produce work or effort in breathing [6, 7].
- *Patient-ventilator interface*: besides discomfort or claustrophobic feelings, there can be leaks that can cause respiratory discomfort. In patients under NIV, leaks have been demonstrated to change breathing pattern and cause patient–ventilator asynchronies [6, 7].

• *Complications of the cardiovascular system:*

- *Pulmonary edema in congestive heart failure*: besides worsening of pulmonary gas exchange, and reducing pulmonary compliance, it has been suggested that J-receptors, responding to vascular distention, are stimulated in this case, being responsible for dyspnea [3].
- *Pulmonary embolism* can cause an increase in physiological dead space and therefore worsen ventilation-perfusion relations [3].
- *Cardiac arrhythmias* especially present in the set of hypoxemia or rapid alterations in pH can also cause feelings of respiratory discomfort [3].
- *Coexisting coronary disease or valvular heart disease* should also be mentioned as aggravating dyspnea [3].
- *Dyspnea due to diseases outside the respiratory and cardiovascular systems.*
- *Anemia* can cause dyspnea through a ventilation-perfusion unbalance [3, 6–8].
- *Iatrogenic (pharmacological):* nonselective beta-blockers and nonsteroidal anti-inflammatory drugs can cause bronchospasm and therefore feeling of chest tightness [3, 6–8].
- *Extrinsic stimuli of respiratory drive*: fever or metabolic acidosis can increase ventilatory drive and cause "air hunger" as described before [3, 6–8].
- *Mental status:* in mechanically ventilated patients, dyspnea is strongly associated with anxiety and relationships can exist in

both directions. Anxiety and pain stimulate the ventilatory drive, increasing dyspnea but also through the affective dimension of dyspnea, since most of the cortical regions activated (limbic or paralimbic) are also known to play an important role in emotions. Besides that, depressed patients may have lower confidence and adherence to therapies adding difficulties [7, 8, 10, 11].

11.2.4 Clinical Relevance of Dyspnea in Mechanically Ventilated Patients

It is known that dyspnea alone has a bad prognostic value in patients with stable COPD. Also, during COPD acute exacerbations, dyspnea is a predictor of hospital mortality [12, 13]. In a more acute setting, in the ICU, it has been shown that dyspnea during invasive ventilation is frequent, often intense and that is correlated with delayed extubation and prolonged ICU stay [5, 7].

In the case of noninvasive ventilation, a large prospective study [5] showed similarities to other studies, moderate-to-severe dyspnea in 55% at admission and 39% after first NIV session in patients with acute respiratory failure. Also showed that dyspnea persisting or not improving after the first NIV session is associated with NIV failure and therefore increased risk of intubation and higher short-term and long-term mortality.

11.3 Conclusion Discussion

Dyspnea is very prevalent and clinically relevant during NIV, and therefore, it should be actively searched and addressed.

Key Major Recommendations

- Dyspnea is a common and disturbing symptom.
- There are three types of dyspnea that are currently considered and best characterized: work or effort in breathing, chest tightness, and air hunger/unsatisfied inspiration.
- Several measuring instruments have been proposed for quantifying dyspnea in daily practice.
- In the presence of dyspnea during NIV, several factors must be considered, starting with the underlying disease and its severity, comorbidities, patient's mental state, ventilator and interface settings, as well as the possibility of complications.
- Dyspnea during NIV is prevalent and is associated with NIV failure, increased risk of intubation, and higher short-term and long-term mortality.

References

1. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185:435–52.
2. Campbell ML, Templin T, Walch J. A respiratory distress observation scale for patients unable to self-report dyspnea. J Palliat Med. 2010;13(3):285–90. https://doi.org/10.1089/jpm.2009.0229.
3. Berliner D, Schneider N, Welte T, Bauersachs J. The differential diagnosis of dyspnoea. Dtsch Arztebl Int. 2016;113:834–45. https://doi.org/10.3238/arztebl.2016.0834.
4. West JB. Pulmonary pathophysiology: the essentials. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2013.
5. Dangers L, Montlahuc C, Kouatchet A, et al. Dyspnoea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact. Eur Respir J. 2018;52:1702637.
6. Schmidt M, Banzett RB, Raux M, et al. Unrecognized suffering in the ICU: addressing dyspnea in mechanically ventilated patients. Intensive Care Med. 2014;40:1–10.
7. Schmidt M, Demoule A, Polito A, et al. Dyspnea in mechanically ventilated critically ill patients. Crit Care Med. 2011;39:2059–65.
8. Decavèle M, Similowski T, Demoule A. Detection and management of dyspnea in mechanically ventilated patients. Curr Opin Crit Care. 2019;25(1):86–94. https://doi.org/10.1097/MCC.0000000000000574.
9. Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypoth-

eses. Respir Physiol Neurobiol. 2009;167(1):53–60. https://doi.org/10.1016/j.resp.2008.07.012.
10. Mahler DA, O'Donnell DE. Neurobiology of dyspnea: an overview. In: Mahler DA, O'Donnell DE, editors. Dyspnea: mechanisms, measurement, and management. 3rd ed. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2014. p. 3–10.
11. de Miranda S, Pochard F, Chaize M, et al. Postintensive care unit psychological burden in patients with chronic obstructive pulmonary disease and informal caregivers: a multicenter study. Crit Care Med. 2011;39(1):112–8. https://doi.org/10.1097/CCM.0b013e3181feb824.
12. Nishimura K, Izumi T, Tsukino M, et al. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 2002.
13. Steer J, Norman EM, Afolabi OA. et al, Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. Throax. 67(2).

Pulmonary Function in Rare Pulmonary Diseases

12

Nilgun Alpay

Abstract

Each year approximately 250 new diseases are discovered and are identified as rare diseases. Rare diseases usually have about 5% of a tendency to involve the pulmonary system. It can be said that although rare diseases sound to be uncommon as their prevalence in a given population is low, there is actually a large number of people who suffer from it.

Keywords

Respiratory function tests · Idiopathic pulmonary fibrosis · Cystic fibrosis · Lymphangioleiomyomatosis · Pulmonary alveolar proteinosis

Abbreviations

CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CT	Computerized tomography
DLCO	Diffuse lung capacity testing
ERV	Expiratory reserve volume
FEV1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
FVC	Forced vital capacity
ICEP	Idiopathic chronic eosinophilic pneumonia
IPF	Idiopathic pulmonary fibrosis
IRV	Inspiratory reserve volume
ISWT	Incremental shuttle walk test
LAM	Lymphangioleiomyomatosis
PAP	Pulmonary alveolar proteinosis
PFT	Pulmonary function tests
RV	Residual volume
SMWT	Six minute walk test
TV	Tidal volume
VC	Vital capacity

12.1 Introduction

The total number of rare diseases is 7000. Only in the European Union, there are about 35 million patients who suffer from one of these 7000 rare diseases. In Europe alone, there are approximately 1–2 million people who suffer from a rare disease that has affected their lungs [1].

Before diving deeper into a couple of these rare pulmonary diseases, pulmonary function and pulmonary function tests (PFT) will be shortly discussed in order to have a better understanding of the pulmonary functions in rare diseases, which is the topic of this article.

N. Alpay (✉)
Cukurova University, Adana, Turkey

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_12

12.2 Discussion and Analysis

12.2.1 Pulmonary Function Tests

Pulmonary function, that is, how well one's lungs work, can be determined through a number of tests. These tests that can all be categorized under pulmonary function tests include devices and techniques such as: spirometry, arterial blood gas analysis, lung diffusion capacity testing, lung volume testing, pulse oximetry, and a 6-min walk test [2].

A closer look into how each one of these tests works and what exactly they measure will be explained below.

Spirometry can measure:

- Tidal volume (TV).
- Forced vital capacity (FVC).
- Forced expiratory volume in 1 s (FEV1).
- Vital capacity (VC).
- Inspiratory reserve volume (IRV).
- Expiratory reserve volume (ERV).

However, it cannot measure residual volume (RV) and, hence, also functional residual capacity (FRC) or total lung capacity (TLC) cannot be measured by a spirometry [2]. The ratio of FEV1 to FVC is an important parameter in staging some pulmonary diseases and also predicting the prognosis.

Arterial blood gas analysis can display the acid-base situation in the blood which is a parameter of how well does the patient gets oxygenized/ventilated. For this reason, as the patient does not need to be awake for this pulmonary function testing, it is commonly used in operating rooms and also on patients who are in the intensive care unit, intubated.

The diffuse lung capacity testing (DLCO) involves the patient inspiring a tracer gas and a small amount of carbon monoxide. This allows the physician to evaluate the predicted diffuse lung capacity which then should be adjusted to the patient's hemoglobin levels.

Previously it was mentioned that the spirometry cannot measure the residual capacity. When results like low tidal volume are obtained in the spirometry, often a lung volume testing is done to determine the residual volume, and the residual volume to total lung capacity as it is an important parameter for obstructive pulmonary diseases.

There are two different ways to measure lung volume. One of them includes the uses of gas like helium or nitrogen. This technique tends not to give accurate results as there can be leakages through the mouthpiece. The other technique is body plethysmography; even though this technique gives more accurate results, it also has its own limitations. Therefore, it is only appropriate to say that whole-body plethysmography is only a relatively better option of measuring the lung volume.

A pulse oximetry is one of the simplest methods of pulmonary function testing.

A six-minute walk test (SMWT) is used to determine the functional exercise capacity of the patients. In this test, the patient is asked to walk for 6 min, and how much they have walked in meters and their oxygen saturation, pulse, and blood pressure are the parameters [3].

These pulmonary function tests are going to be the tools to display the pulmonary functions of the patients who suffer from rare pulmonary diseases. The rare diseases that will be discussed in this article are as follows: idiopathic pulmonary fibrosis, lymphangioleiomyomatosis, pulmonary alveolar proteinosis, idiopathic chronic eosinophilic pneumonia, cystic fibrosis, and alpha 1 antitrypsin deficiency.

12.2.2 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) can be simply defined as the progressive scarring of the lung tissue due to an unknown reason. Five out of 10,000 people are diagnosed with it every year; although it is a rare condition, it still means that about 400,000 people get diagnosed with IPF each year in Europe. These epidemiological data also support that IPF patients make up for the majority of interstitial lung disease patients as IPF is the most common of them. Although the exact cause of this disease still remains unclear, a couple of genetic mutations have been associated

with IPF. For the diagnosis and prediction of progression, pulmonary function tests like spirometry are often used in IPF [4].

The data obtained from spirometry on IPF patients often suggest a restrictive pulmonary disease pattern and a reduced diffusion capacity for carbon monoxide; however, if there is an obstructive pattern, the coexistence of other pulmonary disorders should be considered. The parameters of the spirometry all seem to reduce in this disease.

The decline in FVC over 10% in a given amount of time, such as 6 months, is a prognosticator. If there is a decrease of more than 10%, then risk of death increases by about 2.5% [4].

Another pulmonary function test used in IPF is the DLCO. This test displays the impaired gas exchange in these patients. It is also used as a prognosticator and it can be said that when the DLCO is smaller than 35%, if DLCO is less than 39% and limited, if DLCO is greater than 40%, and when the decline in DLCO in a year is greater than 15%, there is increased mortality.

Also, a 6-min walk test is clinically used for IPF patients to see their capacity for exercise. The desaturation being below 88% is a marker for increased mortality [5].

12.2.3 Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a disease that affects more than one system and is seen in women. Proliferation of abnormal cells namely LAM cells result on cysts in the lungs or in the lymphatic and also various typesof tumoral grown. Although the diagnosis is based on X-ray, computerized tomography (CT), and biopsies, pulmonary function tests like spirometry, diffuse lung capacity, and 6-min walk are used for assessing the pulmonary effects and the severity of this rare disease, which occurs in 1 in 6000 births.

Spirometry reveals a reduced FEV1, and the DLCO is also reduced in these patients [6].

Exercise testing like the 6-min walk can display if there is gas impairment or hypoxia, even when the lung functions seem to be within the normal limits.

A trend showing a decline in FEV1 and DLCO for more than 5–10 percent-year would be present when the LAM is aggressive. On the other hand, it is also possible for patients to have a slower loss of function which can take many years before it interrupts daily activities. For this reason, regular pulmonary function testing in patients with LAM is important to define the severity of the disease at that given time for necessary measures to be taken [7].

12.2.4 Pulmonary Alveolar Proteinosis

Pulmonary Alveolar Proteinosis (PAP) is a rare disease in which the type 2 alveoli secrete excessive surfactant and this surfactant builds up causing difficulty in breathing. The disease can affect people of any age; however, it is mostly seen in people aged between 30 and 50 years. About 7 out of one million people are affected by PAP. There are three main types of PAP; congenital, autoimmune, and secondary. Pulmonary function tests such as spirometry and diffuse lung capacity testing are used for diagnosis and prognosis.

These tests on PAP patients can reveal reduced total lung capacity and reduced forced vital capacity indicating a restrictive pattern on those who are severe cases. Others usually have normal readings for FVC and TLC. Diffuse lung capacity test is done periodically as a frequent drop on the diffusing capacity of the lung is a bad prognosticator for the patient [8].

12.2.5 Idiopathic Chronic Eosinophilic Pneumonia

Idiopathic chronic eosinophilic pneumonia (ICEP) is a very rare disease that accounts for 0% to 2.5% of all interstitial lung diseases. It presents with chronic respiratory symptoms and eosinophilia, either or both alveolar and blood. Although the diagnosis is not through the pulmonary function tests, they are used to determine whether the disease has a restrictive or obstructive pattern. ICEP is seen in about one-third to

half of the patients with asthma, and those who have asthma often present with the obstructive pattern. Spirometry can also remain within the normal limits in one-third of the patients. The DLCO is also reduced. Arterial blood gas analysis is also used in these patients and it often reveals moderate hypoxia [9].

12.2.6 Cystic Fibrosis

Cystic fibrosis (CF) is caused by mutations on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The main role of this protein is to take part in the hydroelectrolytic flux. When this protein is altered, it results in abnormal exocrine secretions.

It affects the lungs, liver, gastrointestinal system, the vas deferens, and as mentioned the exocrine glands. CF is characterized by progressive lung disease, malabsorption, malnutrition, diabetes, sinusitis, and growth retardation.

Pulmonary function tests are not traditionally used for the diagnosis of CF; however, they are used to see the prognosis of the disease. The most common test that is used in these patients is the multibreath washout test as this test is more sensitive than spirometry. This technique is also considered to be better than a body plethysmograph [10].

Exercise tests are also used in this group of patients. It can be said that a recent study done by Saglam et al. brought a new look to the exercise tests on CF patients. Their study comparing a 6-min test with an incremental shuttle walk test has revealed that the incremental shuttle walk test is more favorable to use on patients with CF. Incremental shuttle walk test (ISWT) was able to display the symptom-related intolerances and predict prognosis better than the SMWT [11].

Because pulmonary manifestation is the leading cause of death in these patients, it is necessary to mention lung transplantation. According to Cystic Fibrosis Foundation consensus guidelines, there are 21 recommendations but Table 12.1 lists only those related to pulmonary function tests.

12.2.7 Alpha 1 Antitrypsin Deficiency

Alpha 1 antitrypsin deficiency is an inherited disorder that has a prevalence of 1–5 out of 10,000 people. The manifestation in the respiratory system is characterized with chronic obstructive pulmonary disease. PFTs are used to keep the physician up to date about the progression of the disease.

Decreased airflow, increased lung volume, and decreased diffusing capacity are displayed through the PFT like spirometry and DLCO [12].

12.3 Conclusion Discussion

In conclusion, it can be said that even though the rare diseases have a low prevalence in the total population of the world/countries, patients who suffer from rare diseases still make a very large number of individuals whose needs should not be neglected as any other patients. For this reason usage of more than a couple of PFTs can be good for patients and physicians as they may have more to display. There is a need for more research and evaluation on this study, either clinical study or meta-analysis and Cochrane study.

12.4 Key Recommendations

- Since pulmonary function tests have been providing a good way to diagnose and stage these diseases which have pulmonary involvement, these tests should be made.
- Not only spirometry but also diffuse lung capacity testing, arterial blood gas analysis, 6-min walk, and other pulmonary function tests must be precisely assessed for every patient.
- It should be thought that the tests in the same group may be superior to each other and, if possible, these tests should be performed. For example, an incremental shuttle walking test (ISWT) may be better than a 6-min walk in determining the prognosis in patients with cystic fibrosis.

Table 12.1 Pulmonary function test-related Cystic Fibrosis Foundation consensus guidelines

Recommendation	% consensus among transplant referral guidelines committee
1. For individuals with CF who are 18 years of age and older: • FEV1 is <50% predicted and rapidly declining (>20% relative decline in FEV1 within 12 months) • FEV1 is <40% predicted with markers of shortened survival • FEV1 is <30% predicted	100%
2. For individuals with CF who are under the age of 18 year: • FEV1 is <50% predicted and rapidly declining (>20% relative decline in FEV1 within 12 months) • FEV1 is <50% predicted with markers of shortened survival • FEV1 is <40% predicted	100%
3. For individuals with CF and an FEV1 < 40% predicted, the CF Foundation recommends an annual 6-min walk test (6MWT), assessment of the need for supplemental oxygen, and venous blood gas to screen for markers of severe disease that may warrant transplant referral	100%
4. For individuals with CF who are 18 years of age and older with FEV1 < 40% predicted, the CF Foundation recommends a baseline echocardiogram to screen for pulmonary hypertension	
5. Regardless of FEV1, when there are markers of shortened survival: • 6MWT distance <400 m • Hypoxemia (at rest or with exertion) • Hypercarbia (PaCO2 > 50 mmHg, confirmed on arterial blood gas) • Pulmonary hypertension (PA systolic pressure > 50 mmHg on echocardiogram or evidence of right N ventricular dysfunction in the absence of a tricuspid regurgitate jet)	100%
6. Adults with CF with a BMI <18 and FEV1 < 40% predicted while concurrently working to improve nutritional status .	100%
7. Individuals with FEV1 < 40% predicted and >2 exacerbations per year requiring IV antibiotics or 1 exacerbation requiring positive pressure ventilation Regardless of FEV1	100%
8. FEV1 < 40% predicted and massive hemoptysis (>240 mL) requiring ICU admission or bronchial artery embolization	100%
9. FEV1 < 40% predicted and pneumothorax	100%

References

1. Harari S. Why we should care about ultra-rare disease. Eur Respir Rev. 2016;25(140):101–3.
2. Tentu AK, Singh S, Laxmivandana R, Singh SJ. Role of pulmonary function tests in the assessment of lung impairment in patients with diffuse parenchymal lung diseases: association with clinicoradiological-histopathological profile. J Clin Diagn Res. 2018;12(11)
3. Sylvester KP, Clayton N, Cliff I, Hepple M, Kendrick A, Kirkby J, et al. ARTP statement on pulmonary function testing 2020. BMJ Open Respir Res. 2020;7(1):e000575.
4. Sauleda J, Núñez B, Sala E, Soriano JBJMS. Idiopathic pulmonary fibrosis: epidemiology, natural history, phenotypes. Med Sci. 2018;6(4):110.
5. du Bois RM, Weycker D, Albera C, Bradford W, Costabel U, Kartashov A, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. 2011.
6. Taveira-DaSilva AM, Hedin C, Stylianou MP, Travis WD, Matsui K, Ferrans VJ, et al. Reversible airflow obstruction, proliferation of abnormal smooth muscle cells, and impairment of gas exchange as predictors of outcome in lymphangioleiomyomatosis. Am J Respir Crit Care Med. 2001;164(6):1072–6.
7. Taveira-DaSilva AM, Pacheco-Rodriguez G, Moss J. The natural history of lymphangioleiomyomatosis: markers of severity, rate of progression and prognosis. Lymphat Res Biol. 2010;8(1):9–19.
8. Riley L, Wang T, Ataya A. Pulmonary alveolar proteinosis (PAP). Am J Respir Crit Care Med. 2019;200(8):P16–P7.
9. Crowe M, Robinson D, Sagar M, Chen L, Ghamande S. Chronic eosinophilic pneumonia: clinical perspectives. Ther Clin Risk Manag. 2019;15:397.
10. Ratjen F, Bell S, Rowe S, Goss C, Quittner A, Bush A. Cystic fibrosis. JNRDP. 2015;1:15010.

11. Saglam M, Vardar-Yagli N, Savci S, Inal-Ince D, Aribas Z, Bosnak-Guclu M, et al. Six minute walk test versus incremental shuttle walk test in cystic fibrosis. Pediatr Int. 2016;58(9):887–93.
12. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 antitrypsin deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJH B, Stephens K, et al., editors. GeneReviews(®). Seattle, WA: University of Washington, Seattle. Copyright © 1993–2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved; 1993.

Chronic Neuromuscular Disorders

13

Michalis Agrafiotis, Stavros Tryfon,
Afroditi Boutou, and Athanasia Pataka

Abstract

Spirometry, respiratory muscles pressures, peak cough flow, and arterial (or capillary) blood gases are the most commonly used pulmonary function tests for the assessment of patients with neuromuscular disorders. These tests can be used for disease monitoring and patient prognostication, as well as for decision-making regarding the initiation of ventilatory support. However, the use of daytime pulmonary function tests as screening tools for the prediction of sleep hypoventilation cannot be recommended in patients with neuromuscular disorders.

Keywords

Vital capacity · Maximum inspiratory pressure · Maximum expiratory pressure · Sniff nasal inspiratory pressure · Peak cough flow · Base excess

Abbreviations

ALS	Amyotrophic lateral sclerosis
BE	Base excess
BG	Blood gases
DMD	Duchenne muscular dystrophy
FRC	Functional residual capacity
FVC	Forced vital capacity
IVC	Inspiratory vital capacity
NIV	Noninvasive ventilation
NMDs	Neuromuscular disorders
PCF	Peak cough flow
PEmax	Maximum static expiratory pressure
PImax	Maximum static inspiratory pressure
REM	Rapid eye movement
SDB	Sleep-disordered breathing
SNIP	Sniff nasal inspiratory pressure
SVC	Slow vital capacity
$tcPCO_2$	Transcutaneous PCO_2
TLC	Total lung capacity
twPdi	Twitch transdiaphragmatic pressure
VC	Vital capacity

M. Agrafiotis (✉) · A. Pataka
Department of Respiratory Failure, "Georgios Papanikolaou" General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Exohi, Greece

S. Tryfon · A. Boutou
Department of Pulmonary Medicine, "Georgios Papanikolaou" General Hospital of Thessaloniki, Exohi, Greece

13.1 Introduction

The term neuromuscular disorders (NMDs) encompass a heterogeneous group of diseases that may affect the upper motor neuron, the lower motor neuron, the peripheral nerves, the neuro-

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_13

muscular junction, and the muscles. Impairment of respiratory muscle function in patients with NMDs leads to various respiratory complications (infections, atelectases, aspiration, ventilatory failure, etc.), which constitute a major cause of morbidity and mortality [1]. From a practical point of view, respiratory muscles are classified into three groups: (1) inspiratory muscles, responsible for ventilatory pump function and the inspiratory cough phase; (2) expiratory muscles, responsible for active expiration and also participating in the compression/expulsion of cough phases; and (3) upper airway muscles, responsible for upper airway patency, deglutition, and the compression in cough phase [2].

Respiratory involvement in patients with NMDs initially manifests during sleep, leading to various sleep-disordered breathing (SDB) events of which sleep hypoventilation is the most prominent. Several studies have demonstrated that the introduction of noninvasive ventilation (NIV) at the early stages of symptomatic sleep hypoventilation is associated with improved survival and quality of life [1]. The diagnosis of sleep hypoventilation requires a comprehensive sleep study, ideally polysomnography complemented by capnography. In addition, a panoply of daytime pulmonary function tests and investigations may assist the clinician in following up, screening, and prioritizing patients with NMDs. These investigations commonly include spirometry, respiratory muscle pressures, peak cough flow (PCF), and arterial (or capillary) blood gases (BGs). In the rest of this chapter, the utility of each of these tests in the management of patients with NMDs will be reviewed.

13.2 Discussion and Analysis of the Main Topic

13.2.1 Spirometry

Spirometry is the hallmark of respiratory investigations in patients with NMDs, with vital capacity (VC) being the most commonly used functional index. The VC maneuver is performed by instructing the subject to take a deep breath and blow forcibly as much air as they can into the spirometer via a mouthpiece (forced vital capacity, FVC). However, a slow maneuver (slow vital capacity, SVC) can be used in patients who become easily fatigued with the forced maneuver, without compromising prognostic classification and clinical decision-making [3]. The VC maneuver is a meticulously standardized test and reference ranges are available across a wide span of ages and different races. Of note, VC is more sensitive than total lung capacity (TLC) in detecting restriction in patients with advanced expiratory muscle weakness [4]. However, it can be influenced by the presence of parenchymal lung and thoracic wall disease, it cannot discriminate between inspiratory and expiratory muscle weakness, and patients with weak mouth muscles may not be able to achieve a good seal around the mouthpiece. In addition, upright VC is fairly insensitive for the diagnosis of respiratory muscle weakness at early disease stages [5], although supine VC can perform better in this aspect [6, 7]. Postural decreases in VC by >15% and >30% have been proposed as cut-off points for the diagnosis of unilateral and bilateral diaphragmatic weakness, respectively [8].

VC has been validated for the prediction of gas exchange disturbances in patients with NMDs. In a study of 81 patients with amyotrophic lateral sclerosis (ALS), a VC <50% could predict the presence of diurnal hypoventilation with a sensitivity of 89% and a specificity of 53% [9]. In a study of 42 patients with various primary myopathies, Ragette et al. defined SDB as a respiratory disturbance index >5 events/hour of total sleep time or >10 events/hours of rapid eye movement (REM) sleep time and "continuous sleep hypoventilation" as a nocturnal transcutaneous PCO_2 ($tcPCO_2$) >50 mmHg for REM sleep and >50% of non-REM sleep time. This study demonstrated that an inspiratory VC (IVC) <25% could discriminate between patients with diurnal ventilatory failure and those without with a sensitivity of 92% and a specificity of 93%. In the same study, an IVC <60% and <40% were fairly accurate in the prediction of SDB onset (sensitivity 91% and specificity 89%) and "continuous sleep hypoventilation" (sensitivity 94% and specificity 79%), respectively [10]. On

the other hand, based on a retrospective study of 131 patients ALS, nocturnal hypoventilation can be present in half of those who did not report dyspnea and had an FVC >75% [11].

Many studies have established the role of VC assessment for prediction of outcome in patients with NMDs. By evaluating data from 1034 ALS patients, Czapliniski et al. demonstrated that an FVC >75% was associated with a median survival of 4.08 years, as opposed to 2.91 years for patients with an FVC <75%; in this study, FVC independently predicted survival after adjustment for demographic characteristics and treatment modalities [12]. On the other hand, an FVC >80% is a predictor of favorable outcome in ALS but only in the short term, that is, within a 3-month period [13]. In a study of 95 ALS patients, a supine FVC <80% was 94.6% sensitive (albeit 17.9% specific) in predicting death and/or tracheostomy within 1 year [7]. Likewise, an IVC <1 L has been associated with a 5-year survival rate of 8% in patients with Duchenne muscular dystrophy (DMD) [14], while an IVC <1.1 L could identify patients at risk for severe chest infections in a retrospective study of children and adolescents with various NMDs [15].

Several scientific groups have proposed various VC cut-off values as indications for NIV commencement in patients with NMDs [16–21] (Table 13.1). For patients with ALS, a VC <80% plus symptoms of hypoventilation or a VC <50% (regardless of the presence of symptoms) is traditionally used for initiating ventilatory support [20, 21].

Table 13.1 Recommended pulmonary function tests cut-off points for NIV initiation in patients with various types of neuromuscular disorders

Test	Pulmonary function tests cut-off points for NIV initiation
Vital capacity	*NMDs:* VC <50% plus symptoms [16] *ALS:* VC <80% plus symptoms or VC <50% [20, 21] *DMD:* VC <30% plus symptoms [17] *Myotonic dystrophy I*: VC <50% [19] *Pompe's disease*: VC <50% plus symptoms [18]
PImax	*NMDs:* PImax <60 cm H_2O plus symptoms [16] *ALS:* PImax <65 cm H_2O in males and <55 cm H_2O in females plus symptoms or PImax <40 cm H_2O [20, 21] *Myotonic dystrophy I*: PImax <60 cm H_2O [19] *Pompe's disease*: PImax <60 cm H_2O plus symptoms [18]
SNIP	*ALS:* SNIP <50 cm H_2O plus symptoms or SNIP <40 cm H_2O [20, 21] *Pompe's disease*: SNIP <40 cm H_2O plus symptoms [18]
Blood gases	*NMDs:* PCO_2 ≥45 mmHg [16] *ALS:* PCO_2 >45 mmHg [21] *Myotonic dystrophy I*: PCO_2 >45 mmHg [19] *Pompe's disease*: PCO_2 >50 mmHg [18]

13.2.2 Respiratory Muscle Pressures

Tests for the assessment of respiratory muscles pressures can be volitional or nonvolitional, and invasive or noninvasive. Volitional noninvasive tests are among the most commonly used in everyday practice for the assessment of respiratory muscle strength in patients with NMDs. These usually include the maximum static inspiratory pressure (PImax), the maximum static expiratory pressure (PEmax), and the sniff nasal inspiratory pressure (SNIP).

PImax and PEmax are measured at the mouth opening using a manometer attached to a valve and a rubber tube or flanged mouthpiece; a 2-mm-diameter leak prevents the subject from closing their glottis during the PImax maneuver and from recruiting their buccal muscles during the PEmax maneuver. The PImax maneuver is performed by instructing the subject to exhale to residual volume through the mouthpiece and then inhale maximally (Mueller maneuver). Conversely, in the PEmax maneuver, the subject inhales to TLC and then exhales maximally (Valsalva maneuver), while the cheeks are supported by the patient's or an assistant's hands. Both PImax and PEmax maneuvers require that the subject maintains the pressure for at least 1.5 s so that the maximum pressure during the first second can be recorded. The measured pressure consists of the respective inspiratory or expiratory respiratory muscle pressure plus the respiratory system elastic recoil pressure. Optimal test performance requires >3 maneuvers

with <10% variability of which the best is registered [4, 8]. Generally, a PImax/PEmax >70 cm H_2O in females and >80 cm H_2O in males exclude clinically significant respiratory muscle weakness [22]. PImax values <60% and <30% have been advocated by experts as clinically relevant cut-off points for the diagnosis of unilateral and bilateral diaphragmatic dysfunction, respectively [8]. Advantages of PImax and PEmax measurements include their relative easiness of performance and the availability of reference values across all age spans. However, both tests depend on subject's effort and cooperation, require a good mouthpiece seal, and are influenced by the respiratory system elastic recoil, although reference values for both tests when performed at functional residual capacity (FRC) have also become available [22].

PImax has been extensively validated for the prediction of diurnal and sleep hypoventilation in patients with NMDs. A PImax <25% could diagnose diurnal hypoventilation with a sensitivity of 83% and a specificity of 55% in nonbulbar ALS patients [9]. In the study by Ragette et al. on patients with primary myopathies, SDB onset was predicted by PImax <46 cm H_2O with a sensitivity of 82% and a specificity of 89% and "continuous sleep hypoventilation" by a PImax <41 cm H_2O with a sensitivity of 95% and a specificity of 65% [10]. Likewise, in the study by Mellies et al. on a mixed population of children and adolescents with various NMDs, PImax values <41 cm H_2O and <25 cm H_2O predicted SDB onset and nocturnal hypoventilation with sensitivities of 87% and 72% and specificities of 43% and 83%, respectively [23]. On the other hand, Toussaint et al. demonstrated that a PImax≤39 cm H_2O had only a moderate accuracy (sensitivity 71% and specificity 54%) in discriminating DMD patients with nocturnal hypercapnia from NIV-naïve DMD patients with 24-hour normocapnia [24]. In addition, in a small study of 19 DMD patients, PImax showed no correlation with sleep hypoventilation; the last defined as a $t_{<90}$ >2% of the total sleep time [25]. Nevertheless, a PImax <67 cm H_2O showed a sensitivity of 85% and a specificity of 27% in identifying ALS patients requiring implementation of NIV based on symptoms of sleep hypoventilation and the presence of sleep hypercapnia [26].

PImax is strongly correlated with VC [24] and has been validated for following up patients with NMDs. In a study of 10 children with DMD, PImax exhibited an earlier decline than VC and reached 67% at 12 years when the spirometric parameters were still within their reference ranges [27]. On the other hand, in a 3-year follow-up study of 33 DMD patients, PImax continued to increase with age despite a drop in VC after the age of 13 [28]. PImax may also play a role in the prediction of outcome for patients with rapidly progressing NMDs. In the study of Baumann et al. on 90 patients with ALS, a PImax <70 cm H_2O predicted 2-year mortality with a sensitivity of 82% and a specificity of 57% [29]. In a report of 95 ALS patients, a PImax <70 cm H_2O was predictive of death or tracheostomy within the first year with a sensitivity of 100% and a specificity of 14.3% [7].

In 1999, a group of experts proposed a PImax <60 cm H_2O combined with symptoms of hypoventilation as an indication for commencement of NIV treatment in patients with NMDs and chest wall disorders [16]. Several other groups have advocated various PImax cut-off values to facilitate clinical decision-making regarding NIV initiation in patients with various types of NMDs [18–21] (Table 13.1).

PEmax measurements have been associated mainly with cough efficacy and susceptibility to respiratory tract infections. A PEmax >60 cm H_2O has been associated with an effective cough, while a PEmax <45 cm H_2O commonly indicates impaired cough efficacy [30]. PEmax has also been correlated with the infection rate and the number of days in antibiotics in children with various NMDs [15]. In addition, PEmax decline may also offer prognostic information in patients with NMDs. In the study by Baumann et al. on ALS patients, a PEmax <70 cm H_2O had a moderate accuracy in predicting death at 2 years (sensitivity 58% and specificity 72%) [29]. In a study of 78 ALS patients, which compared various tools for the assessment of respiratory muscle weakness, PEmax was among the predictors of 3-year ventilator-free and absolute survival [13].

SNIP is measured with a plug wedged into the nostril and connected to a manometer, while the other nostril remains unoccluded. The SNIP maneuver is a quasi-dynamic test performed by instructing the subject to sniff maximally and sharply from FRC; more than 10 attempts are sometimes required to obtain reproducible results [4, 8]. A SNIP >60 cm H_2O in men and >50 cm H_2O in women is thought to rule out clinically significant inspiratory muscle weakness [22]. Based on expert opinion, SNIP values<60% and 30% are associated with unilateral and bilateral diaphragmatic dysfunction, respectively [8]. Advantages of the SNIP maneuver include the intuitive nature of the test and its applicability in patients with weak mouth muscles. However, SNIP appears to be limited as an index of inspiratory muscle strength in ALS patients with bulbar disease [9, 31], can be influenced by the presence of nasal congestion, it may underestimate esophageal pressure in chronic obstructive pulmonary disease [4], and it is unclear whether leaving unoccluded the contralateral nostril is the optimal measurement technique [32].

Several studies have indicated that SNIP decline may be an early sign of respiratory deterioration in patients with NMDs. In a small report involving 16 ALS patients with normal VC (>80%), both SNIP and PImax were abnormally low (67% and 69%, respectively). However, although all variables showed a similar linear decline, fewer people were able to perform the VC and PImax maneuvers at advanced disease stages [33]. In the study by Neve et al. on children and adolescents with DMD, SNIP and VC increased initially with age, but SNIP decline occurred earlier than VC (at 10.5 vs. 12.5 years, respectively); however, PImax showed no change with age. Patients with lower SNIP and VC were more likely to be started on NIV before the age of 17. This advantage was not observed in Becker's muscular dystrophy, a dystrophinopathy of a less severe phenotype, in which PImax, VC, and SNIP continued to increase until the age of 20 [28]. Khirani et al. also evaluated retrospective longitudinal data from 48 boys with DMD between 6 and 19 years old. VC started to decline after the age of 13–14 at a rate of 5% predicted/year, while SNIP decreased after the age of 10 at a rate of 5.4% predicted/year [34]. In another study, involving 16 patients with types 2 and 3 spinal muscular atrophy, SNIP and VC (but not PImax) exhibited the steepest decline over a 10-year follow-up period [35].

SNIP has been advocated as a screening tool for identifying ALS patients with diurnal hypercapnia and SDB. In the study by Lyall et al., a SNIP <32% could predict diurnal hypercapnia in nonbulbar ALS patients with a sensitivity of 85% and a specificity of 81% [9]. In study involving 98 ALS patients, Morgan et al. reported a stronger correlation of SNIP with the presence and severity of sleep hypoxemia compared to VC and PImax [36]. Likewise, in a prospective polysomnographic study of 31 ALS patients, SNIP was inversely correlated with various indices of sleep hypoxemia, while patients with a SNIP <60 cm H_2O had a significantly higher time spent with a SaO_2 <90% (t_{90}), as opposed to those with higher SNIP values (11.1 vs. 1.2%, respectively) [37]. In addition, in the study by Tilanus et al., a SNIP <45 cm H_2O could discriminate between ALS patients with an indication of NIV and those without with a sensitivity of 87% and specificity of 40%; while, among various tools (VC, PImax, PEmax, and PCF), SNIP exhibited the steepest decline 3 months before NIV commencement [26]. In a more recent study on 47 patients with ALS (11 with bulbar-onset disease), a SNIP <28 cm H_2O predicted sleep hypoventilation ($tcPCO_2$, >49 mmHg) with a sensitivity of 93.8% and a specificity of 85%, but only in nonbulbar patients [31].

SNIP offers prognostic information for the outcome of patients with ALS. In the study by Morgan et al., the sensitivities and specificities for the prediction of 6-month mortality were 97% and 79% for a SNIP <40 cm H_2O and 58% and 97% for a VC <50%; the respective numbers for a PImax <40 cm H_2O were 100% and 76%, but fewer patients were able to perform the PImax maneuver at the final disease stages [36]. Likewise, in a study of 100 ALS patients, a SNIP <34 cm H_2O predicted death and/or tracheostomy within the first year with a sensitivity of 75% and a specificity of 72%; the respective values for a

VC <76% were both 58%, however, the inclusion of VC did not contribute significantly to the overall prognostic model [38].

Various cut-off SNIP values have been proposed by expert groups for the management of various types of NMDs, with a SNIP <40 cm H_2O commonly considered an indication for NIV commencement in patients with ALS and Pompe's disease [18, 20, 21] (Table 13.1).

Invasive assessments of respiratory muscle strength are not commonly used outside clinical research. However, in the study by Lyall et al., sniff transdiaphragmatic pressure (measured using esophageal and gastric balloons while the subject performs a sniff maneuver) had the highest accuracy in predicting diurnal hypoventilation in nonbulbar ALS patients [9]. Polkey et al. also demonstrated that, among various indices of respiratory muscle strength, twitch transdiaphragmatic pressure (twPdi) (obtained by phrenic nerve magnetic stimulation) was the single best predictor of 3-year ventilator-free and total survival in patients with ALS, followed by SNIP [13]. In addition, in the study by Khirani et al. on patients with DMD, cough gastric pressure (measured using a gastric balloon while the patient is instructed to cough) shows the steepest decline (together with FVC and SNIP) over a 10-year follow-up period [34]. According to experts, twPdi values <20 cm H_2O and <10 cm H_2O are indicators of unilateral and bilateral diaphragmatic dysfunction, respectively [8].

13.2.3 Peak Cough Flow

Normal cough consists of three phases: an inspiratory phase up to 85–90% of TLC; a compression phase in which the glottis closes and the expiratory muscles are contracted, and an expulsion phase when the glottis opens and cough is produced [30]. Therefore, effective cough requires cooperation of all three groups of respiratory muscles and an impaired cough is a sign of advanced respiratory muscle disease. Cough efficacy is commonly estimated by PCF, which is the maximum expiratory flow generated when the subject is instructed to inhale maximally and cough as forcibly as they can into a peak flow meter, spirometer, or pneumotachograph. A mouthpiece or a mask interface can be used and >3 maneuvers with a <5% variability are required, of which the best is registered. A PCF <160 L/min indicates impaired secretion management and high risk for tracheostomy decannulation failure; and a PCF <270 L/min has been associated with a high risk for acute respiratory failure and intubation during trivial respiratory tract infections [1, 8].

Being an index of global respiratory muscle strength, PCF has been evaluated as a screening tool to assess outcomes in patients with NMDs. In a prospective study of 32 ALS patients with no indication for NIV at stable condition, a PCF <174 L/min had a sensitivity of 77% and a specificity of 71% in predicting requirement for ventilatory support during the course of an acute respiratory tract infection [39]. In a study of 110 ALS patients, a PCF <386 L/min at the first visit discriminated patients with an indication of nocturnal NIV with a sensitivity of 88% and a specificity of 36% [26]. According to the results of another study, a rapid PCF decline (>25%/year) is an independent predictor of survival in ALS patients [40].

13.2.4 Arterial (or Capillary) Blood Gases

Assessment of arterial (or capillary) BGs is of paramount importance in the evaluation of patients with NMDs. The main role of BGs testing is for the diagnosis of diurnal hypoventilation (commonly defined as a PCO_2 >45 mm Hg), which is a definite indication for NIV [16, 18, 19, 21]. In addition, an increased alveolar-arterial difference should point toward a concurrent parenchymal lung disease. The main disadvantages of BGs assessment are the invasive nature of the test and the low sensitivity of PCO_2 at early disease stages [9, 10].

Some authors have investigated the utility of BGs testing for predicting sleep hypoventilation. In the study by Hukins and Hillman on 19 patients with DMD, a PCO_2 ≥45 mm Hg was 91% sensitive and 75% specific for the diagnosis of sleep

hypoventilation ($t_{<90}$ >2%); the respective values for a base excess (BE) ≥4 mmol/L were 55% and 100% [25]. Likewise, in the study by Crescimanno et al. on 47 ALS patients, a BE >2.3 mmol/L was 93.75% sensitive and 65% specific for the prediction of sleep hypoventilation ($tcPCO_2$, >49 mmHg); however, this advantage was evident only in nonbulbar patients [31]. In a report of 250 ALS patients, early morning BE, bicarbonate, and $t_{<90}$ were all independent predictors of sleep hypoventilation (a $tcPCO_2$ >49 mmHg or an overnight increase in a $tcPCO_2$ >10 mmHg). However, an early morning BE >3 mmol/L had a sensitivity of 61% and a specificity of 71% in identifying patients with sleep hypoventilation; this sensitivity increased to 83% when BE was combined with a $t_{<90}$ >5 min [41].

13.3 Conclusions

Daytime pulmonary function tests are essential for monitoring disease progress, prognostication, and clinical decision-making in patients with NMDs. Several cut-off points available from the literature may assist the clinician in selecting patients who would benefit from NIV. However, daytime pulmonary function tests are of limited value in predicting sleep hypoventilation, mainly because of low specificity. Differences in patient populations, types of NMDs, groups of involved muscles, as well as definitions of sleep hypoventilation may partly account for this limitation.

Key Major Recommendations

- Daytime pulmonary function tests commonly used for monitoring patients with NMDs include spirometry, tests of respiratory muscle strength (PImax, PEmax, and SNIP), PCF, and BGs.
- Daytime pulmonary function tests offer significant information regarding disease progress and functional decline in patients with NMDs.
- SNIP is an index of early functional decline in patients with ALS and DMD.
- Daytime pulmonary function tests are commonly used as screening tools to identify NMD patients who may benefit from NIV initiation.
- The use of daytime pulmonary function tests for the prediction of sleep hypoventilation in patients with NMDs cannot be recommended.

References

1. Voulgaris A, Antoniadou M, Agrafiotis M, Steiropoulos P. Respiratory involvement in patients with neuromuscular diseases: a narrative review. Pulm Med. 2019;2019:2734054.
2. Agrafiotis M, Kousta A, Nikolaou K. Mechanical insufflation-exsufflation devices: principles and technology. In: Esquinas AM, editor. Mechanical ventilators for non-invasive ventilation. Nova Science Publishers, Inc. New York; 2020.
3. Calvo A, Vasta R, Moglia C, Matteoni E, Canosa A, Mattei A, et al. Prognostic role of slow vital capacity in amyotrophic lateral sclerosis. J Neurol. 2020;267(6):1615–21.
4. American Thoracic Society/European Respiratory society. ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518–624.
5. Braun NM, Arora NS, Rochester DF. Respiratory muscle and pulmonary function in polymyositis and other proximal myopathies. Thorax. 1983;38(8):616–23.
6. Lechtzin N, Wiener CM, Shade DM, Clawson L, Diette GB. Spirometry in the supine position improves the detection of diaphragmatic weakness in patients with amyotrophic lateral sclerosis. Chest. 2002;121(2):436–42.
7. Schmidt EP, Drachman DB, Wiener CM, Clawson L, Kimball R, Lechtzin N. Pulmonary predictors of survival in amyotrophic lateral sclerosis: use in clinical trial design. Muscle Nerve. 2006;33(1):127–32.
8. Laveneziana P, Albuquerque A, Aliverti A, Babb T, Barreiro E, Dres M, et al. ERS statement on respiratory muscle testing at rest and during exercise. Eur Respir J. 2019;53(6)
9. Lyall RA, Donaldson N, Polkey MI, Leigh PN, Moxham J. Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. Brain. 2001;124(Pt 10):2000–13.
10. Ragette R, Mellies U, Schwake C, Voit T, Teschler H. Patterns and predictors of sleep disordered breathing in primary myopathies. Thorax. 2002;57(8):724–8.
11. Prell T, Ringer TM, Wullenkord K, Garrison P, Gunkel A, Stubendorff B, et al. Assessment of pulmonary function in amyotrophic lateral sclerosis: when can polygraphy help evaluate the need for non-invasive ventilation. J Neurol Neurosurg Psychiatry. 2016;87(9):1022–6.
12. Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease

progression in an ALS clinic population. J Neurol Neurosurg Psychiatry. 2006;77(3):390–2.
13. Polkey MI, Lyall RA, Yang K, Johnson E, Leigh PN, Moxham J. Respiratory muscle strength as a predictive biomarker for survival in amyotrophic lateral sclerosis. Am J Respir Crit Care Med. 2017;195(1):86–95.
14. Phillips MF, Quinlivan RC, Edwards RH, Calverley PM. Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med. 2001;164(12):2191–4.
15. Dohna-Schwake C, Ragette R, Teschler H, Voit T, Mellies U. Predictors of severe chest infections in pediatric neuromuscular disorders. Neuromuscul Disord. 2006;16(5):325–8.
16. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. Chest. 1999;116(2):521–34.
17. Birnkrant DJ, Bushby KM, Amin RS, Bach JR, Benditt JO, Eagle M, et al. The respiratory management of patients with duchenne muscular dystrophy: a DMD care considerations working group specialty article. Pediatr Pulmonol. 2010;45(8):739–48.
18. Boentert M, Prigent H, Várdi K, Jones HN, Mellies U, Simonds AK, et al. Practical recommendations for diagnosis and management of respiratory muscle weakness in late-onset Pompe disease. Int J Mol Sci. 2016:17(10).
19. Boentert M, Cao M, Mass D, De Mattia E, Falcier E, Goncalves M, et al. Consensus-based care recommendations for pulmonologists treating adults with myotonic dystrophy type 1. Respiration. 2020;99(4):360–8.
20. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the quality standards Subcommittee of the American Academy of neurology. Neurology. 2009;73(15):1218–26.
21. Rimmer KP, Kaminska M, Nonoyama M, Giannouli E, Maltais F, Morrison DL et al. Home mechanical ventilation for patients with amyotrophic lateral sclerosis: a Canadian thoracic society clinical practice guideline. 2019.
22. Fitting JW. Volitional assessment of respiratory muscle strength. Monaldi Arch Chest Dis. 2012;77(1):19–22.
23. Mellies U, Ragette R, Schwake C, Boehm H, Voit T, Teschler H. Daytime predictors of sleep disordered breathing in children and adolescents with neuromuscular disorders. Neuromuscul Disord. 2003;13(2):123–8.
24. Toussaint M, Steens M, Soudon P. Lung function accurately predicts hypercapnia in patients with Duchenne muscular dystrophy. Chest. 2007;131(2):368–75.
25. Hukins CA, Hillman DR. Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. Am J Respir Crit Care Med. 2000;161(1):166–70.
26. Tilanus TBM, Groothuis JT, TenBroek-Pastoor JMC, Feuth TB, Heijdra YF, Slenders JPL, et al. The predictive value of respiratory function tests for noninvasive ventilation in amyotrophic lateral sclerosis. Respir Res. 2017;18(1):144.
27. Gayraud J, Ramonatxo M, Rivier F, Humberclaude V, Petrof B, Matecki S. Ventilatory parameters and maximal respiratory pressure changes with age in Duchenne muscular dystrophy patients. Pediatr Pulmonol. 2010;45(6):552–9.
28. Nève V, Cuisset JM, Edmé JL, Carpentier A, Howsam M, Leclerc O, et al. Sniff nasal inspiratory pressure in the longitudinal assessment of young Duchenne muscular dystrophy children. Eur Respir J. 2013;42(3):671–80.
29. Baumann F, Henderson RD, Morrison SC, Brown M, Hutchinson N, Douglas JA, et al. Use of respiratory function tests to predict survival in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2010;11(1–2):194–202.
30. Kravitz RM. Airway clearance in Duchenne muscular dystrophy. Pediatrics. 2009;123(Suppl 4): S231–5.
31. Crescimanno G, Sorano A, Greco F, Canino M, Abbate A, Marrone O. Heterogeneity of predictors of nocturnal hypoventilation in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2021;22(1–2):46–52.
32. Murray D, Rooney J, Campion A, Fenton L, Hammond M, Heverin M, et al. Longitudinal analysis of sniff nasal inspiratory pressure assessed using occluded and un-occluded measurement techniques in amyotrophic lateral sclerosis and primary lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(7–8):481–9.
33. Fitting JW, Paillex R, Hirt L, Aebischer P, Schluep M. Sniff nasal pressure: a sensitive respiratory test to assess progression of amyotrophic lateral sclerosis. Ann Neurol. 1999;46(6):887–93.
34. Khirani S, Ramirez A, Aubertin G, Boulé M, Chemouny C, Forin V, et al. Respiratory muscle decline in Duchenne muscular dystrophy. Pediatr Pulmonol. 2014;49(5):473–81.
35. Khirani S, Colella M, Caldarelli V, Aubertin G, Boulé M, Forin V, et al. Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3. Eur J Paediatr Neurol. 2013;17(6):552–60.
36. Morgan RK, McNally S, Alexander M, Conroy R, Hardiman O, Costello RW. Use of sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. Am J Respir Crit Care Med. 2005;171(3):269–74.
37. Carratù P, Cassano A, Gadaleta F, Tedone M, Dongiovanni S, Fanfulla F, et al. Association between low sniff nasal-inspiratory pressure (SNIP) and sleep disordered breathing in amyotrophic lateral sclerosis: preliminary results. Amyotroph Lateral Scler. 2011;12(6):458–63.

38. Capozzo R, Quaranta VN, Pellegrini F, Fontana A, Copetti M, Carratù P, et al. Sniff nasal inspiratory pressure as a prognostic factor of tracheostomy or death in amyotrophic lateral sclerosis. J Neurol. 2015;262(3):593–603.
39. Sancho J, Servera E, Bañuls P, Marin J. Predictors of need for noninvasive ventilation during respiratory tract infections in medically stable, non-ventilated subjects with amyotrophic lateral sclerosis. Respir Care. 2015;60(4):492–7.
40. Matsuda C, Shimizu T, Nakayama Y, Haraguchi M. Cough peak flow decline rate predicts survival in patients with amyotrophic lateral sclerosis. Muscle Nerve. 2019;59(2):168–73.
41. Boentert M, Glatz C, Helmle C, Okegwo A, Young P. Prevalence of sleep apnoea and capnographic detection of nocturnal hypoventilation in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2018;89(4):418–24.

14 Continuous Noninvasive Ventilator Support (Neuromuscular Disorders)

Candela María Rodríguez Mejías
and Juan Pablo Valencia Quintero

Abstract

In the course of neuromuscular diseases, respiratory failure may occur and, therefore, it may be necessary to start support with noninvasive mechanical ventilation. The most commonly used mode is noninvasive positive-pressure ventilation (NPPV). The correct selection of appropriate interface, respirator, and ventilation mode is essential for the success of this technique; thus, reducing days of hospital stay and mortality.

Keywords

Noninvasive positive-pressure ventilation · Neuromuscular disease · Interfaces · Noninvasive ventilation

Abbreviations

CPAP	Continuous positive airway pressure
NIV	Noninvasive ventilation
NPPV	Noninvasive positive-pressure ventilation

14.1 Introduction

Neuromuscular diseases, both acute and chronic, can cause weakness of the respiratory and airway muscles. Often this weakness is progressive and triggers respiratory failure, which is the leading cause of death in these patients [1]. So, noninvasive ventilation support is often necessary in patients with neuromuscular disease. The most common is the use of noninvasive positive-pressure ventilation (NPPV) [2]. For the use of this type of support, it is essential to know the functional anatomy of the respiratory system, as well as the pathophysiology of the underlying neuromuscular disease and its progression [3]. To be successful in this technique, a correct choice of equipment to be used is essential, taking into account the needs and wishes of the patient, the familiarity of the doctor who prescribes it, and the availability of equipment. Support with noninvasive ventilation can be applied with a variety of interfaces, ventilators, and ventilator settings [2] that must be tailored for each individual patient. Ventilatory interventions can improve morbidity and mortality in patients with neuromuscular diseases [1, 4].

C. M. Rodríguez Mejías (✉) · J. P. Valencia Quintero
Intensive Care Unit, Hospital Universitario Virgen de las Nieves, Granada, Spain

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_14

14.2 Discussion and Analysis of the Main Topic

Neuromuscular diseases can be classified according to their mode of acquisition (congenital or acquired disorders), disease onset (acute or chronic), disease progression (slow, variable, rapidly progressive, or nonprogressive), and site of neuraxial affection (spinal cord, neuropathic, neuromuscular junction, and myopathic) (Table 14.1) [3].

The main mechanisms of respiratory failure in neuromuscular diseases are the inability to effectively clear respiratory secretions, failure of upper or lower airway patency, and hypoventilation related to poor effort and lung restriction [3]. Inspiratory muscle weakness results in atelectasis from maintained low lung volumes and inability to clear secretions. As the disease progresses, chest wall compliance may be reduced by respiratory muscle atrophy. This situation may worsen hypoventilation which manifests first at night, later in day time, and finally as chronic hypercapnic acidosis. Sleep-disordered breathing and hypoxia may also occurred [3]. If airway (bulbar) and expiration muscles are affected, then aspiration and atelectasis may happen because of the inadequate clearance of oral and respiratory secretions.

Signs to observe to diagnose ventilatory insufficiency include orthopnea, tachypnea, paradoxical breathing, hypophonia, use of accessory respiratory muscles, and cyanosis. Symptomatic hypercapnic patients present with morning headaches, fatigue, sleep disturbances, and hypersomnolence [5].

Noninvasive ventilation (NIV) should be offered to patients with any neuromuscular disease when there is daytime hypercapnia or symptomatic nocturnal hypoventilation [6].

NIV consists of the application of continuous or intermittent positive pressure through an interface that covers the nose, mouth, or both. The main modes of ventilation in neuromuscular diseases are continuous positive airway pressure (CPAP) and bilevel positive airway pressure [3].

As the disease progresses, noninvasive nocturnal ventilation may be insufficient to control daytime respiratory failure. It may be necessary for NIV support 24 h a day.

There are some general contraindications for NIV:

- Respiratory arrest.
- Low level of consciousness (Glasgow coma scale of ≤8/15).
- Inability to protect airway.
- Massive upper gastrointestinal bleeding or active vomiting.
- Hypotension or shock.
- Multiorgan failure.
- Inability to fit mask.

Table 14.1 Examples of neuromuscular diseases that cause respiratory failure

	Acute	Chronic
Spinal cord/neuropathic disorders	– Guillain-Barre syndrome – Cervical spinal cord injury – Multiple sclerosis – Acute poliomyelitis – Transverse myelitis	– Spinal cord injury – Motor neuron disease – Amyotrophic lateral sclerosis – Charcot-Marie-tooth disease
Neuromuscular junction disorders	– Myasthenia gravis – Lambert-Eaton myasthenic syndrome – Congenital myasthenic syndrome – Botulism – Organophosphorus poisoning	
Myopathic disorders		– Muscular dystrophies – Myotonic dystrophy – Inflammatory myopathies – Congenital and metabolic myopathies

In neuromuscular diseases, NIV is contraindicated when bulbar affection exists, when the acute respiratory failure is present with quick deterioration of gas exchange, or when invasive mechanical ventilation is required [3]. In other contraindications like persistent hypoxia, severe hypercapnia with acidosis, no patient cooperation, agitation, seizures, high cervical spinal cord injury, acute phases of neuropathic/myelopathic diseases, etc., NIV can be applied with a variety of interfaces, ventilators, and ventilator settings.

14.2.1 Interfaces

An interface is a mask or device that directs airflow into the upper airway. Choosing the correct interface has a great impact on the comfort and adaptation of the patient to the NIV. The ideal interface would have to be transparent, lightweight, low dead space, easy to secure, easy to clean, adequate seal with low facial pressure, nonallergenic, inexpensive, anti-asphyxia mechanism, quickly removable, variety of sizes, and adaptable to variations in facial anatomy [2]. There are several types of interfaces. Here are some advantages and disadvantages of the most used models: [2, 4, 7–8]

- Mouth piece/lip cover: Used for day and night NIV with or without a lip cover phalange and straps to retain the mouthpiece.
- Nasal masks: The most popular interfaces for chronic administration of NPPV. They provide greater patient comfort and better preservation of speech and swallowing than other interfaces with low risk of aspirations, easier secretion clearance, less dead space, easy to fit, and secure. However, they have mouth leak, mouth dryness, nasal irritation, and rhinorrhea.
- Oronasal masks: They should fit just above the junction of the nasal bone and cartilage to just below the lower lip. They are the interfaces most often used to administer NPPV to patients with acute respiratory failure. This kind of interface helps to mouth leak control and it is more effective in mouth breathers but it has increased dead space, increased aspiration risk, and increased difficulty speaking and eating.
- Total face mask: Less facial skin breakdown and easier to fit, however, it has potential for orthodontic injury, greater dead space, potential for drying of the eyes, and cannot deliver aerosolized medications.

Leak through the mouth is common with a nasal mask. This can affect comfort, cause dry mouth, and result in less effective ventilation. If persistent mouth leak occurs, an oronasal mask is often needed. In some patients, nasal interfaces can be used during the daytime and oronasal mask is used at night to minimize mouth leak and improve sleep quality [2].

Appropriate headgear is needed to maintain correct position of the mask. Most modern masks designed specifically for NPPV use cloth straps and Velcro to secure the mask [2]. Fitting the headgear too tightly is a common mistake and it may not improve the fit and may decrease patient comfort. It should be possible to pass at least one finger between the headgear and the face.

A very frequent problem is facial skin breakdown, which most commonly appears on the bridge of the nose. In order to avoid this issue, it is important to not strap the mask too tightly and a correct choose of mask size. Small-to-moderate leaks are compensated by ventilators modes.

14.2.2 Ventilator and Ventilator Settings

When choosing the ventilator, a series of considerations must be taken into account, such as oxygen delivery (acute care), monitoring, leak compensation, trigger, and cycle, coupled with patient's breathing pattern, rebreathing, alarms portability, cost, etc.

Studies that have directly compared pressure- and volume-limited ventilators have found similar efficacies in terms of supporting gas exchange and patient adherence. In terms of patient satisfaction, volume-limited ventilators may induce more gastrointestinal side effects, whereas pressure-

limited ventilators are generally perceived by patients as being more comfortable [7, 8].

Negative pressure ventilators have several disadvantages compared to NPPV (i.e., less portable, harder to apply, and apt to exacerbate obstructive sleep apnea). Consequently, they are seldom used today and are of mainly historical interest [8].

Abdominal respirators were useful in patients with bilateral diaphragmatic paralysis. However, the relative ineffectiveness of these devices in patients with acute illness or abnormal body habitus limits their use. Once again, these have been replaced by NPPV for the most part [8].

NPPV is the most common noninvasive ventilation mode. It requires an interface and a positive pressure ventilator. In contrast to ventilation via an invasive airway, NPPV uses an open breathing circuit, is inherently leaky, and depends upon patient cooperation to achieve ventilatory assistance [7].

NIV should be considered the preferred option for ventilation even when ventilation is required 24 h per day. Elective tracheostomy ventilation may be considered and it is dependent on regional resources and careful discussion with the patient and caregivers [6]. No extent of inspiratory or expiratory muscle failure or ventilator dependence is in itself an indication for tracheotomy. The only indication for tracheostomy for patients with ventilatory pump failure is inability to cooperate with NIV or to prevent the aspiration of airway secretions that cause a drop in the peripheral oxygen saturation below 95% despite NIV [8].

It is also very important to combine NIV with cough-assist devices in order to obtain an optimal clearance of respiratory secretions, but this is not the aim of this chapter.

14.3 Conclusion Discussion

The use of NPPV in patients with neuromuscular diseases is nowadays very common, and it is likely to expand. The selection of equipment for NPPV is mainly based on patient's needs, the physiopathology of the respiratory failure, the desires of the patient, and the equipment available. Support with noninvasive ventilation can be applied with a variety of interfaces, ventilators, and ventilator settings that must be tailored for each individual patient. The right choice is essential for the patient's comfort and therapy success.

Key Major Recommendations

- NIV should be offered to patients with any neuromuscular diseases when there is daytime hypercapnia or symptomatic nocturnal hypoventilation.
- Signs to observe for ventilatory insufficiency include orthopnea, tachypnea, paradoxical breathing, hypophonia, use of accessory respiratory muscles, cyanosis. Symptomatic hypercapnic patients present with morning headaches, fatigue, sleep disturbances, and hypersomnolence.
- The adaptation of the patient to the ventilator and interfaces is crucial for the success of this therapy.
- NIV should be considered the preferred option for ventilation even when ventilation is required 24 h per day.
- It is very important to combine NIV with cough-assist devices in order to obtain an optimal clearance of respiratory secretions.

References

1. Servera E, Sancho J, Zafra MJ, et al. Alternatives to endotracheal intubation for patients with neuromuscular diseases. Am J Phys Med Rehabil. 2005;84(11):851.
2. Hess DR. Noninvasive ventilation in neuromuscular disease: equipment and application. Respir Care. 2006;51(8):896–911.
3. Regunath H, Whitacre T, Whitt SP. Non-invasive ventilation in neuromuscular diseases. In: Govindarajan R, Bollu P, editors. Sleep issues in neuromuscular disorders. Springer: Cham; 2018. p. 129–38. https://doi.org/10.1007/978-3-319-73068-4_9.
4. Bach JR, Gonçalves MR, Hon A, et al. Changing trends in the management of end-stage neuromuscular respiratory muscle failure: recommendations of an international consensus. Am J Phys Med Rehabil. 2013;92(3):267–77.

5. Bach JR. Noninvasive respiratory management of patients with neuromuscular disease. Ann Rehabil Med. 2017;41(4):519–38.
6. McKim DA, Road J, Avendano M, et al. Home mechanical ventilation: a Canadian thoracic society clinical practice guideline. Can Respir J. 2011;18(4):197–215.
7. Bach JR. Continuous noninvasive ventilatory support for patients with respiratory muscle dysfunction. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA; 2020.
8. Hill NS, Kramer NR. Types of noninvasive nocturnal ventilatory support in neuromuscular and chest wall disease. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA; 2020.

Chest Wall Disorders

15

Meliha Orhon Ergün and Seniyye Ulgen Zengin

Abstract

Patients with severe chest wall deformity have a decreased capacity of the respiratory muscles due to rib cage deformity that can cause chronic respiratory failure. In recent years, NIMV treatment has become popular in patients with chronic respiratory failure due to chest-wall deformity. NIMV treatment can improve quality of sleep, physical activity, and quality of life.

Keywords

NIMV · Chest wall disorders · Chronic respiratory insufficiency

Abbreviations

FBN1	Fibrillin-1
KS	Kyphoscoliosis
MFS	Marfan syndrome
NIMV	Noninvasive mechanical ventilation
NIPPV	Noninvasive positive-pressure ventilation
NIV	Noninvasive ventilation

M. Orhon Ergün (✉) · S. U. Zengin
Department of Anesthesiology and Reanimation, Marmara University School of Medicine, Istanbul, Turkey

15.1 Introduction

The chest wall is an important part of the human ventilatory pump [1]. Chest wall disorders develop a group of diseases and deformities that affect the rib cage, respiratory muscles, and abdomen. The physiologic evidence of these disorders is restriction caused by a poorly stretchable chest wall. Chest wall deformities disturb the rib cage expansion and result in restrictive defect (decrease TLC). Costosternal and costovertebral junctions demonstrate true synovial joints with synovial spaces that simplify expansion of the chest wall during inspiration [2]. Respiratory muscle weakness is unavoidable in many congenital neuromuscular and chest wall diseases. These diseases result in chronic ventilatory insufficiency, but flail chest causes acute respiratory insufficiency [2]. Elastic loads on the respiratory muscles are cause of ventilatory failure in chest wall diseases (Table 15.1).

Table 15.1 Causes contributing to respiratory failure in chest wall diseases

Increased elastic loads on respiratory muscles owing to:
(a) Decreased distensibility of the chest wall
(b) Age-related decrease in chest wall compliance
Coexisting lung dysfunction
Sleep breathing abnormalities
Mechanical disadvantage of the diaphragm
Age-related impairment of respiratory muscle function

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_15

15.1.1 Kyphoscoliosis

Kyphoscoliosis is the most common leading cause of respiratory failure among rib cage deformities. The term scoliosis describes lateral deformation of the spine in the coronal plane with an angle of spinal curvature greater than 10°. Scoliosis can influence the thoracic, lumbar, or thoracolumbar vertebrae. Kyphosis represents extreme forward curvature and mostly complicates scoliosis [3].

Kyphoscoliosis is the cause of respiratory failure among all chest wall disorders [2]. Lung volumes have been broadly studied in kyphoscoliosis. Schneevogt declared a remarkable reduction in vital capacity [4]. The reduction in vital capacity is significant when the dorsal spine is affected and patients have Cobb angle greater than 100°. Moreover, decrease in vital capacity is directly related to decrease in total lung capacity [2].

Severe deformities can cause significant cardiopulmonary failure. Early kyphoscoliosis can result in rapid decrease in pulmonary functions, and lead to pulmonary hypertension and respiratory insuffiency [2]. Restrictive disorders that restrict lung expansion, resulting in a decreased lung volume, an increased work of breathing, and inadequate ventilation and/or oxygenation can be seen in patient who have angles of 90° or greater. Exercise intolerance and dyspnea are early sign of kyphoscoliosis. Oxyhemoglobin saturation decreases with exercise and distance walked [5]. Noninvasive positive-pressure ventilation increases alveolar pressure, reduces symptoms, sets up pulmonary function, and reduces mortality and pulmonary artery pressure [6].

15.1.2 Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disease characterized by inflammation of the spine and sacroiliac. Extraarticular organs can be involved, including the respiratory (chest wall), eyes, cardiovascular, and kidneys [7].

Ankylosing spondylitis has limited rib cage expansion due to stiffening and fusion of the costovertebral and sternoclavicular articulations. Intercostal muscles can be atrophy with advanced disease [8]. This stiffening decreases respiratory compliance [9]. The rib cage is stiff and the abdomen is compliant, and chest wall inflation is primarily accomplished through diaphragmatic displacement of the abdomen [8].

Congenital chest wall deformities: they are anomalies that occur with the absence, shortness, bifurcation, and fusions of one or more ribs or cartilage, and can be seen in different forms such as pectus excavatum, pectus carinatum, Poland syndrome, sternal defects, and isolated rib cartilage anomalies [10]. It should be kept in mind that the most common of these deformities is pectus excavatum, and thoracic deformities may be accompanied by other skeletal system deformities, cardiovascular, gastrointestinal, and genitourinary anomalies [11].

15.1.3 Pectus Excavatum

Bauhinus in 1594 complaints of pulmonary compression, dyspnea, paroxysmal cough by evaluating the clinical findings of a patient with chest deformity, this deformity has defined [12].

15.1.4 Pectus Carinatum

This deformity was first described by Brodkin in 1949, which is the second-most common chest wall deformity after pectus excavatum. It is in the form of anterior protrusion of the thoracic wall. “Chondro-gladios,” “Chondro-manubrial,” and “Mixed (pectus carinatum + pectus excavatum) type” separated [10].

15.1.5 Poland Syndrome

Poland syndrome is accompanied by major and minor components and has a complete etiology. It is a rare syndrome that is not known, and its major components include the pectoralis major muscle agenesis, agenesis or hypogenesis of the minor pectoral muscle, syndactyly, hand anomalies such as brachydactyly, brachydactyly, and

acromelia, as well as subcutaneous tissue hypoplasia, 2–5. agenesis of costal cartilages, less hair growth in the chest and axillary area, scapula Nowadays, accompanied by minor components such as deformity, many variants [10].

15.1.6 Marfan Syndrome

Marfan syndrome (MFS) is a connective tissue disease with an estimated incidence of 2–6 persons per 100000.1 It is caused by mutations in the gene fibrillin-1 (FBN1) on chromosome 15 that encodes the FBN1 protein, which is an essential part of the connective tissue of the cardiovascular and musculoskeletal systems [13].

The syndrome includes several body systems, mostly the cardiovascular, ocular, and skeletal systems. MFS' effect on the skeletal system involves arachnodactyly, dolichostenomelia, generalized ligamentous laxity, and chest, spine, pelvic, and foot deformities. A deformity of the thoracic cage (pectus carinatum or excavatum) and scoliosis are among the most common features of MFS and exist to some degree in approximately 60% of the patients. Pulmonary involvement in MFS can be found in approximately 63% of the patients.

15.1.7 Sternal Defects

Sternal defects that comprise a broad spectrum of deformities of the sternum, heart, and upper abdominal wall, from simple sternum defect to total absence of chest wall potentially fatal. Pectus excavatum and carinatum deformities are most common deformities than sternal defects [10].

Sternal defects:

1. Sternal cleft (cleft sternum):
   (a) Partial.
   (b) Total.
   (c) With vascular dysplasia.
2. Ectopia cordis.
   (a) Cervical.
   (b) Thoracic.
3. Pentalogy of Cantrell (thoracoabdominal ectopia cordis).

15.1.8 Costa and Cartilage Anomalies

Costa and cartilage anomalies usually do not cause dysfunction and are deformities seen as synostoses, bridging, and agenesis of cartilages. Severe deformities may occur at later ages in cases with more than one costa agenesis. **In these cases**, when the deformity is not corrected, the expected Since the life span is short, correction should be made at the early ages of 2–3 years [10].

15.2 Discussion and Analysis of Main Topic

Chest wall disease is a frequent cause of respiratory failure. Noninvasive positive-pressure ventilation (NIPPV) is an established treatment in chronic respiratory failure due to chest wall deformity (CWD). A recent Cochrane systematic review including four current studies with a total of 51 patients confirmed improvements in symptoms of hypoventilation, daytime hypercapnia, and nocturnal oxygenation [14].

Supplemental oxygen and NIV are used to treat gas exchange abnormalities. Acute respiratory failure is a frequent and life-threatening complication in chest wall disorders. Noninvasive ventilation (NIV) has been used to acute and chronic respiratory failure. Morbidity and mortality decrease with NIV as compared to invasive ventilation, and has been suggested for acute respiratory failure in immunosuppressed patients [15]. NIV prevents endotracheal intubation, lung infections, barotrauma, tracheal stenosis, as well as the need for tracheostomy, and reduces the length of stay in ICU [15]. When the maximum inspiratory pressure is less than 60 cm H_2O, or forced vital capacity is less than 50% predicted, or if nocturnal arterial oxygen saturation is less than 88% for more than 5 consecutive minutes, NIV is started in progressive conditions [15].

Most ventilator modes are either pressure or volume controlled, each with potential advantages and disadvantages. Since the 1980s, volume-targeted NIV has been the predominant

type of NIV used in patients with chronic respiratory failure due to chest wall deformity. In recent years, however, pressure-targeted NIV has become a widely accepted alternative. Volume ventilation includes a predetermined set tidal volume but, in the presence of interface leakage, the set volume is not guaranteed, which, theoretically at least, is a problem, particularly during sleep when NIV is conventionally applied. Pressure-targeted NIVM delivers a predetermined pressure that results in different tidal volumes depending on chest wall compliance, airway resistance, and patient effort. Volume-targeted and pressure-targeted long-term NIV are equally effective in patients with chest wall deformity [16]. However, there are no guidelines for the choice between volume NIV and pressure NIV in these patients. Assuming equal effectiveness of gas exchange, a difference in time to adequate patient adjustment to NIV could help us determine whether pressure NIV or volume NIV is a better choice.

Improvement in gas exchange in patients with CDW after the application of NIV is an important factor that is closely related to the prognosis. The need to check blood gases early in the follow-up of these patients seems reasonable because the initial response observed during hospital admission should be reconsidered once ventilation is used at home. Thus, delayed gasometric evaluation of NIHMV efficacy may better reflect the patients' response to NIHMV. In previous reports, it was shown that a relatively low $PaCO_2$ value a few months after beginning NIV was a good prognostic factor for hospitalization due to respiratory insufficiency and for mortality in patients with chronic restrictive ventilatory failure. A recent study suggested that $PaCO_2$ level of 50 mmHg at 1 month after starting NIHMV and the presence of comorbid conditions are risk factors for mortality in patients with chest wall disease. In a novel study, it was reported that PaO_2 value after 12 months of NIV may be a useful marker for predicting the prognosis in patients with restrictive thoracic disease who are receiving long-term NIV therapy. It suggested that PaO_2 rather than the $PaCO_2$ after 12 months of NIV was an independent prognostic factor for mortality [17].

15.3 Conclusion Discussion

Current evidence about the therapeutic benefit of mechanical ventilation is of very low quality, but directionally consistent, suggesting alleviation of the symptoms of chronic hypoventilation, improvement in survival, and reduced risk of unplanned hospitalization.

Key Major Recommendations

- Chest wall deformities disturb the rib cage expansion and result in restrictive defect (decrease TLC).
- Volume-targeted and pressure-targeted long-term NIV are equally effective in patients with chest wall deformity.
- Improvement in gas exchange in patients with CDW after the application of NIV is an important factor that is closely related to the prognosis.

References

1. George E, Tzelepis MD. Chest wall diseases respiratory pathophysiology. Clin Chest Med. 2018;39:281–96.
2. Al-Qadi MO. Disorders of the chest wall clinical manifestation. Clin Chest Med. 2018;39:361–75.
3. Bergofsky EH. Respiratory failure in disorders of the thoracic cage. Am Rev Respir Dis. 1979;119:643–69.
4. Alves VL, Avanzi O. Objective assessment of the cardiorespiratory function of adolescents with idiopathic scoliosis through the six-minute walk test. Spine. 2009;34(25):E926–9.
5. Gonzalez C, Ferris G, Diaz J, et al. Kyphoscoliotic ventilatory insufficiency: effects of long-term intermittent positive pressure ventilation. Chest. 2003;124(3):857–62.
6. Taurag JD, Chhabra A, Calbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med. 2016;374(26):1379–90.
7. Romagnoli I, Giglotti F, Galarducci A, et al. Chest wall kinematics and respiratory muscle action in ankylosing spondylitis patients. Eur Respir J. 2004;24(3):453–60.
8. Aqqarwal AN, Gupta D, Wanchu A, et al. Use of static lung mechanics to identify early pulmonary involvement in patients with ankylosing spondylitis. J Postgrad Med. 2001;47(2):89–94.

9. Yavuzer Ş. Konjenital Göğüs Ön Duvarı Deformiteleri. Toraks Cerrahi Bülteni Eylül: Türk Toraks Derneği; 2011. p. 164–8.
10. Yavuzer Ş. Toraks Deformiteleri. AÜ Tıp Fak Yayınları Ankara; 2008.
11. Radunovic A, Anne D, Rafiq MK, Brassngton R, Mustfa M. Mechanical ventilation for amyotrophic lateral sclerosis/ motor neuron disease. Cochrane Database Syst Rev. 2017;(10).
12. Annane D, Orlikowski D, Chevret S, Chevrolet JC, Raphael JC. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev 2014, 12.
13. Otremski H, Widmann RF, Di Maio MF, Ovadia. The correlation between spinal and chest wall deformities and pulmonary function in Marfan syndrome. J Child Orthop. 2020;14:343–8. https://doi.org/10.1302/1863-2548.14.200076.
14. Annane D, Chevrolet JC, Chevret S, et al. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev. 2000;2:CD001941.
15. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J. 2002;20(2):480–7. https://doi.org/10.1183/09031936.02.00404002.
16. Struik FM, Duiverman ML, Meijer PM, Nieuwenhuis JA, Kerstjens HAM, Wijkstra PJ. Volume-targeted versus pressure-targeted noninvasive ventilation in patients with chest-wall deformity: a pilot study. Respir Care. 2011;56(10):1522–5. https://doi.org/10.4187/respcare.01043.
17. Chihara Y, Tsuboi T, Sumi K, Sato A, Oga T, Chin K. Low levels of PaO_2 after long-term noninvasive ventilation are a poor prognostic factor in patients with restrictive thoracic disease. Intern Med. 2019;58(9):1243–50. https://doi.org/10.2169/internalmedicine.1860-18.

Chronic Obstructive and Cystic Fibrosis Respiratory Disorders

16

Inês Moreira, Ana Magalhães, and Mariana Cabral

Abstract

This chapter will address the pathogenic mechanisms of the disease, the way they influence lung function, and how it interferes with the way noninvasive ventilation is applied in COPD patients.

Keywords

COPD · Pulmonary function · Obstructive airway disease · NIV

Abbreviations

ATS/ERS	American Thoracic Society/European Respiratory Society
BTS	British Thoracic Society
CAT	COPD Assessment Test
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
DLCO	Diffusing capacity for carbon monoxide
DLCO/VA	DLCO divided by alveolar volume (transfer coefficient—KCO)
ECCS	European Community of Coal and Steel
EFL	Expiratory flow limitation during tidal breathing
EPAP	Expiratory positive airways pressure
FEV 1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IC	Inspiratory capacity
LLN	Lower limits of normal
mMRC	Modified Medical Research Council Dyspnea Scale
NIV	Noninvasive ventilation
PEEP	Positive end-expiratory pressure
RV	Residual volume
TLC	Total lung capacity
VC	Vital capacity

16.1 Introduction

Chronic obstructive pulmonary disease (COPD) is projected to be the third leading cause of death by 2020 [1]. It is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities caused by long-term exposure to noxious particles and gases, particularly the ones from cigarette smoke

I. Moreira (✉) · A. Magalhães · M. Cabral
Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_16

[2], and also biomass fuel exposure and air pollution [1]. The development of COPD is also related to host factors—genetics (alpha 1 antitrypsin deficiency), airway hyperresponsiveness, and poor lung growth during childhood [1].

The symptoms include dyspnea, cough, and sputum production. The disease is punctuated by periods of acute worsening of symptoms called exacerbations [1].

COPD is characterized by an abnormal inflammatory response in the lungs, structural changes, and poorly reversible airflow obstruction. There is an enhanced or abnormal innate and adaptive immune response that results in mucous hypersecretion (chronic bronchitis), lung tissue destruction (emphysema), and disruption of normal repair and defense mechanisms causing airway inflammation and fibrosis (bronchiolitis). These pathological changes result in increased resistance to airflow in small airways, increased compliance of the lungs, air trapping and progressive airflow obstruction [2].

The airflow obstruction in COPD is measured by spirometry, which is the gold standard for diagnosis and also helpful in assessing the severity of the disease and managing it once the diagnosis is made [1].

COPD is associated with other chronic diseases, which increase its morbidity and mortality [1].

16.2 Discussion and Analysis of the Main Topic

16.2.1 Pathogenesis

Three main processes are involved in the pathogenesis of COPD: inflammation, imbalance between proteases and antiproteases, and oxidants and antioxidants (oxidative stress) in the lungs [2].

16.2.1.1 Inflammatory Cells and Mediators

COPD is characterized by increased number of inflammatory cells and its activity in the lungs: neutrophils, macrophages, and T lymphocytes (CD8 and CD4, with an increase in CD8/CD4 ratio). These inflammatory cells release a variety of cytokines and mediators that participate in the disease process. They are present in the sputum, airways, bronchial glands, smooth muscle, lung parenchyma, or bronchoalveolar lavage fluid [3] of smokers and COPD patients and are related to disease severity [2].

Inflammatory mediators involved in COPD are as follows:
Leukotriene B4, a neutrophil, and T-cell chemoattractant
Chemotactic factors such as the CXC chemokines interleukin 8 and growth-related oncogene, which are produced by macrophages and epithelial cells
Proinflammatory cytokines such as tumor necrosis factor and interleukins 1 and 6
Growth factors such as transforming growth factor, which may cause fibrosis in the airways either directly or through release of another cytokine and connective tissue growth factor

In addition, B-lymphocytes are also increased in the peripheral airways and within lymphoid follicles, possibly as a response to chronic infection of the airways [2]. Increased eosinophil numbers have also been reported in COPD patients during exacerbations, but their relevance to COPD changes is less clear than in asthma and their presence is associated with corticosteroid response [3].

In general, the extent of the inflammation is related to the degree of the airflow obstruction [2].

16.2.1.2 Protease and Antiprotease Imbalance

Cigarette smoke and inflammation lead to the inflammatory cells release of a combination of proteases and inactivation of several antiproteases, resulting in oxidative stress [2].

Proteases and antiproteases involved in COPD are follows:	
Proteases	Antiproteases
Serine proteases	Alpha 1 antitrypsin
Neutrophil elastase	Secretory leukoprotease inhibitor
Cathepsin G	Elafin

Protease 3	Cystatins
Cysteine proteases	Tissue inhibitors of MMP (TIMPs 1–4)
Cathepsins B, K, L, and S	
Matrix metalloproteases (MMP-8, MMP-9, and MM-12)	

16.2.1.3 Oxidative Stress

Oxidative metabolism is overactivated in COPD [3]. Sources of oxidants include cigarette smoke and reactive oxygen and nitrogen species released from inflammatory cells. It, therefore, leads to amplification of inflammation by enhancing transcription factor activation (such as nuclear factor kB) and, hence, gene expression of proinflammatory mediators [2].

16.2.2 Pathophysiology

The described pathogenic mechanisms result in the pathological changes found in COPD patients which result in physiological abnormalities.

16.2.2.1 Mucous Hypersecretion and Ciliary Dysfunction

The hypersecretion is due to squamous metaplasia, increased number of globet cells, and increased size of bronchial submucosal glands in response to chronic irritation by noxious particles and gases [2]. Ciliary dysfunction is due to squamous metaplasia of epithelial cells and results in an abnormal mucociliary escalator and difficulty in expectorating [2]. These changes result in chronic productive cough [2].

16.2.2.2 Airflow Obstruction and Hyperinflation or "Air Trapping"

Airflow obstruction occurs mainly in the small conducting airways (<2 mm in diameter) because of the inflammatory exudates, airway remodeling, and loss of the lung elastic recoil due to destruction of alveolar walls [1]. The airways obstruction progressively traps air during expiration, resulting in hyperinflation during exercise, which reduces the inspiratory capacity and, therefore, the functional residual capacity during exercise [2]. These changes result in dyspnea and limited exercise capacity [2].

16.2.2.3 Gas Exchange Abnormalities

Emphysema is characterized by a loss of lung parenchyma with a possibly increased apoptosis of endothelial and epithelial alveolar cells. The bronchial epithelium in the airways is modified—squamous cell metaplasia, globet cell hyperplasia, and loss of CC10+ cells (Clara cells) [3]. In advanced disease, this abnormal distribution of ventilation/perfusion ratio results in deficient delivery of oxygen to the bloodstream [1]. These changes result in respiratory insufficiency (arterial hypoxemia with or without hypercapnia).

16.2.2.4 Pulmonary Hypertension

Also in advanced disease, pulmonar hypertension develops due to pulmonar arterial constriction (as a result of hypoxia), endothelial dysfunction, remodeling of the pulmonary arteries (smooth muscle hypertrophy and hyperplasia), and destruction of the pulmonar capillary bed [3]. Structural changes in the pulmonar arterioles result in persistent pulmonar hypertension and right ventricular hypertrophy or enlargement and dysfunction (cor pulmonale) [2].

16.2.3 Respiratory Physiology

The first definition of chronic bronchitis and emphysema occurred at "Ciba Guest Symposion" in 1959. Chronic bronchitis was defined as the presence of productive cough for at least 3 months in 2 consecutive months and emphysema as the widening of airspace. The definition of these two components was based on clinic and imaging, and pulmonary function assessment was not recommended. This concept persisted until the late 1990s. Only in the first GOLD (Global Initiative for Chronic Obstructive Lung Disease) orientation in 2001 did it require the diagnosis and classification of the disease based on lung function, by means of spirometry [4].

Pulmonary function testing has three components: (1) spirometry, (2) lung volumes, and (3) diffusing capacity of the lung for carbon monoxide (DLCO) [4].

16.2.3.1 Spirometry

Spirometry is the gold standard for making the diagnosis of COPD [1]. It is also helpful in assessing the severity of the disease and managing it once the diagnosis is made [4]. In symptomatic patients, spirometry can help determine whether the patient's symptoms are due to respiratory disease or other conditions [4].

Spirometry consists of (1) forced vital capacity (FVC), (2) forced expiratory volume in 1 s (FEV1), and (3) FEV1/FVC ratio measured by forced exhalation maneuver [1]. These measurements are expressed in liters, reported as percent of predicted for that patient according to reference values [4]. In Europe, the combined reference equations published in the 1993 European Respiratory Society (ERS) statement are often used for people aged 18–70 years, with a height range 155–195 cm in males, and 145–180 cm in females, but a new Europe-wide study to derive updated reference equations for lung function is needed [6].

COPD is characterized by obstruction to expiratory flow, resulting in decrease in FEV1 [5]. The decline in FEV1 in COPD is mainly related to thickening of the walls of small conducting airways and obstruction of these airways by mucous exudates [3]. If the FEV1 is decreased disproportionately to the FVC, a diagnosis of COPD is made [4].

However, the definition of obstruction remains controversial. Current GOLD guidelines continue to define airflow limitation by a fixed FEV1/FVC threshold of 0.7, independently of age and sex. American Thoracic Society (ATS)/ERS guidelines on COPD recommend that FEV1 is referred to VC (vital capacity) rather than just FVC and the cut-off value of this ratio is set at the fifth percentile of the normal distribution rather than at a fixed value of 0.7 [6]. British Thoracic Society (BTS) guidelines define it as FEV1/FVC <0.7 but requiring also a FEV1 < 80% predicted. Many studies converge to challenge the diagnostic value of GOLD criteria due to the false-negative rate in young subjects at risk and the false-positive rate in older patients [3], thus overdiagnosing the elderly with no history of exposure to noxious particles or gases [6]. This is due to FE1V/FVC ratio declining with normal aging [4]. The lower limits of normal (LLN) seems to be more reliable for defining obstruction, particularly for screening purposes [3].

In obstructive lung disease, such as COPD, the expiratory limb takes on a coved shape [3].

Spirometry can also be used to quantify COPD severity [4].

Classification of airflow limitation severity in COPD		
In patients that have FEV1/FVC<0.7 after bronchodilator in spirometry:		
GOLD 1	Mild	FEV 1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV 1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV 1 < 50% predicted
GOLD 4	Very severe	FEV 1 < 30% predicted

In patients with respiratory diseases, a low FEV1/VC, even when FEV1 is within the normal range, predicts morbidity and mortality [6]. But FEV1 may sometimes fail to properly identify the severity of a defect, especially at the very severe stages of the diseases. FEV1 correlates poorly with symptoms and may not, by itself, accurately predict clinical severity or prognosis for individual patients [6]. Patients should also undergo assessment of dyspnea using mMRC or symptoms using CAT and their history of exacerbations should be recorded. FEV1 correlates with the risk of exacerbations. Exacerbating patients have a faster decline in FEV1. FEV1 is associated with pulmonary, cardio, and cerebrovascular mortality [4].

Lung hyperinflation and the presence of expiratory flow limitation during tidal breathing may be useful in categorizing the severity of lung function impairment [6].

Spirometry can also be used to manage COPD—it can guide therapy for COPD, enable monitoring of progression, help determinate prognosis, and estimate long-term survival [4].

16.2.3.2 Lung Volumes

Lung volumes are related to body size, and standing height is the most important correlating variable. In practice, many USA and European laboratories use the reference equations for TLC, FRC, and RV recommended by the 1995 ATS/ERS workshop or by the ECCS in 1993 [6]. Lung volumes are measured by helium dilution, nitrogen washout, or body plethysmography. The last one has become the gold standard because the first two underestimate total lung capacity in COPD [3].

Lung volumes consist of total lung capacity (TLC), residual volume (RV), and functional residual capacity (FRC) [3].

Measurement of lung volumes is not mandatory to identify an obstructive defect. It may, however, help to disclose underlying disease and its functional consequences. For example, an increase in TLC, RV, or the RV/TLC ratio above the upper limits of natural variability may suggest the presence of emphysema or other obstructive diseases, as well as the degree of lung hyperinflation [6].

Emphysema destroys lung tissue, leading to loss of elastic recoil, which allows the lungs to be stretched to abnormally large volumes [3]. This plus severe airflow obstruction and dynamic mechanisms causes FRC, RV, TLC, and RV/TLC increase. The degree of hyperinflation parallels the severity of airway obstruction. On one hand, lung hyperinflation is of benefit because it modulates airflow obstruction, but, on the other hand, it causes dyspnea because of the increased elastic load on inspiratory muscles [7].

Resting lung hyperinflation, measured as inspiratory capacity (IC)/TLC, is independent predictor of respiratory and all-cause mortality in COPD patients [7].

In addition, in either severe obstructive or restrictive diseases, tidal expiratory flow often impinges on maximum flow. This condition, denoted as expiratory flow limitation during tidal breathing (EFL), is relatively easy to measure in practice by comparing tidal and forced expiratory flow-volume loops. Its clinical importance is that it contributes to increased dyspnea, puts the inspiratory muscles at a mechanical disadvantage, and causes cardiovascular side effects. Although there is currently no sufficient evidence to recommend the routine use of measurements of hyperinflation or EFL to score the severity of lung function impairment, they may be helpful in patients with disproportionate dyspnea [7].

In patients with moderate-to-severe COPD, end-expiratory lung volume increases under conditions of greater minute ventilation (e.g., exercise)—dynamic hyperinflation. It is key determinant of symptomatology and exercise intolerance in COPD. Reduced elastic recoil, loss of alveolar attachments, and increased airway resistance are the mechanical factors traditionally invoked to explain the occurrence of dynamic hyperinflation in COPD [7].

16.2.3.3 DLCO

DLCO is a measure of how easily carbon monoxide (CO) molecules transfer from the alveolar gas to the hemoglobin of the red cells in the pulmonar circulation [4]. No specific set of equations is generally recommended. The lower fifth percentile of the reference population should be used as LLN for DLCO and KC. Adjustments of DLCO for changes in hemoglobin and carboxyhemoglobin are important. The relationship between DLCO and lung volume is not linear, so DLCO/VA or DLCO/TLC does not provide an appropriate way to normalize DLCO for lung Volume [6].

Interpreting the DLCO, in conjunction with spirometry and lung volumes assessment, may assist in diagnosing the underlying disease [6].

For instance, normal spirometry and lung volumes associated with decreased DLCO may suggest early emphysema. In the presence of airflow obstruction, a decreased DLCO makes this hypothesis more robust [6].

DLCO decreases with increasing severity of disease [1]. This is because in emphysema, the lung has lost alveoli, resulting in lower surface area available for diffusion. There is also a loss of capillary bed which can also increase

DLCO. When DLCO falls below 55% of predicted, the patient should undergo a PM6M to determine if oxygen is required [4].

Dregree of severity of decresead DLCO	
Degree of severity	DLCO % predicted
Mild	>60% and <LLN
Moderate	40–60%
Severe	<40

16.2.4 Noninvasive Ventilation in COPD

The role of noninvasive ventilation (NIV) in COPD is to decrease work of breathing and improve respiratory mechanics through effects on several pathophysiologic abnormalities present in severe COPD [1].

In severe COPD, the lungs are hyperinflated because of the presence of emphysema and small airway disease that together contribute to increased lower airway resistance [4]. Hyperinflation together with other pathobiological mechanisms related to muscle dysfunction in severe COPD lead to diaphragm muscle atrophy [5]. The combination of diaphragm muscle atrophy and the airflow obstruction central to COPD pathophysiology leads to increased respiratory muscle load [5].

Besides, hypoxemia can impact skeletal muscle strength and endurance, and chronic hypercapnia can induce skeletal muscle dysfunction. Chronic hypercapnia also suppresses innate immunity. A reduction in CO2 levels may have an effect in reducing COPD exacerbations leading to hospital admissions [3].

The goal of NIV in COPD is to offset the diaphragmatic dysfunction (achieve control of spontaneous breathing with near abolition of diaphragm activity); therefore, reducing chronic hypercapnia [5].

	Respiratory physiological abnormalities in COPD	Benefit conferred by NIV
Obstructive airway disease	Increased inflammatory cells producing mucus plus increased smooth muscle contributing to airway constriction	Positive pressure keeps airways open
Alveolar destruction	Destruction of alveoli secondary to emphysema plus loss of elastic recoil contributing to hyperinflation	EPAP optimized to overcome intrinsic PEEP to decrease respiratory muscle load
Diaphragmatic dysfunction	Atrophy from hyperinflation, limited excursion to support ventilation, increased respiratory muscle load secondary to increased airway resistance, and diaphragm atrophy	High-intensity pressure support ventilation with backup rate reduces diaphragm effort and controls mechanism of breathing

Patients with COPD and respiratory failure, whether acute or chronic, have a poorer prognosis than patients without respiratory failure. NIV has been shown to be a useful tool in both the acute hospital and chronic home care setting [1]. NIV has been well established as the gold standard therapy for acute decompensated respiratory failure complicating an acute exacerbation of COPD with reduced mortality and intubation rates compared to standard therapy. However, NIV has been increasingly used in other clinical situations such as for weaning from invasive ventilation and to palliate symptoms in patients not suitable for invasive ventilation. The equivocal evidence for the use of NIV in chronic hypercapnic respiratory failure complicating COPD has recently been challenged with data now supporting a role for therapy in selected subgroups of patients [5].

16.3 Conclusion Discussion

COPD is a common condition with high morbidity and mortality. COPD is characterized by an abnormal inflammatory response in the lungs, structural changes, and poorly reversible airflow obstruction. Spirometry is the gold standard for making the diagnosis. The goal of COPD management is to improve a patient's functional status and quality of life by improving symptoms preventing the recurrence of exacerbations and preserving optimal lung function. Oxygen therapy when indicated and smoking cessation may reduce mortality. No treatments aside from lung transplantation have been shown to significantly improve lung function or decrease mortality. NIV has been shown to be a useful tool in both the acute hospital and chronic home care setting, acting at the level of obstructive airway disease, alveolar destruction, and diaphragmatic dysfunction.

Key Major Recommendations

- Three main processes are involved in the pathogenesis of COPD: inflammation, an imbalance between proteases and antiproteases, and imbalance between oxidants and antioxidants (oxidative stress) in the lungs.
- Spirometry is the gold standard for making the diagnosis. COPD is characterized by obstruction to expiratory flow, resulting in decrease in FEV1.
- Emphysema destroys lung tissue, leading to loss of elastic recoil, which allows the lungs to be stretched to abnormally large volumes—hyperinflation. In patients with moderate-to-severe COPD, end-expiratory lung volume increases under conditions of greater minute ventilation (e.g., exercise)—dynamic hyperinflation.
- NIV has been shown to be a useful tool in both the acute hospital and chronic home care setting, acting at the level of obstructive airway disease, alveolar destruction, and diaphragmatic dysfunction.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Pocket guide to COPD Diagnosis, Management and Prevention. A guide for healthcare professionals. 2020 Edition. www.goldcopd.org. Accessed Sept 2020.
2. MacNee W. ABC of chronic obstructive pulmonar disease - Pathology, pathogenesis and pathopysiology. BMJ. 2006;332:1202–4.
3. Bourdin A, Burgel PR, Chanez P, et al. Recent advances in COPD: pathophysiology, respiratory physiology and clinical aspects, including comorbidities. Eur Respir Rev. 2009;18:198–212.
4. Bailey KL. The importance of assessment of pulmonar function in COPD. Med Clin North Am. 2012;96:745–52.
5. Coleman JM, Wolfe LF, Kalhan R. Noninvasive ventilation in chronic obstructive pulmonary disease. Am Thorac Soc. 16:1091–8.
6. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
7. Marini JJ. Dynamic hyperinflation and pulmonary inflammation: a potentially relevant relationship? Am J Respir Crit Care Med. 2011;184:756–62.

Cystic Fibrosis

17

Inês Moreira, Ana Magalhães, and Mariana Cabral

Abstract

This chapter will address the pathogenic mechanisms of the disease, the way they influence lung function, and how it interferes with the way noninvasive ventilation is applied in CF patients.

Keywords

Cystic fibrosis · Pulmonary function · Obstructive airway disease · NIV

Abbreviations

ADA	American Diabetes Association
CF	Cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFTR	CF transmembrane conductance regulator
CPET	Cardiopulmonary exercise testing
FEV 1	Forced expiratory volume in 1 s
FOT	Forced oscillation techniques
FRC	Functional residual capacity
LCI	Lung clearance index
NIV	Noninvasive ventilation
PES	Pediatric Endocrine Society

I. Moreira (✉) · A. Magalhães · M. Cabral
Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

17.1 Introduction

Cystic fibrosis (CF) affects more than 80,000 people worldwide. It occurs in 1 out of 3500 births of Caucasians and northern Europeans. It is a life-threatening genetic disorder that causes an accumulation of thick and viscous mucus secretions in various organ systems, most commonly the pulmonary, gastrointestinal, and genitourinary. The median survival for individuals with CF has increased to 40 years of age. Although CF is a multiorgan system disease, its effects on the pulmonary system are the leading cause of patient morbidity and mortality [1].

17.2 Discussion and Analysis of the Main Topic

17.2.1 Pathogenesis

CF is caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene. The CFTR protein produced by this gene regulates the movement of chloride and sodium ions across epithelial cell membranes [2]. When mutations occur in one or both copies of the gene, ion transport is defective and results in a buildup of thick mucus throughout the body, leading to respiratory insufficiency along with many other systemic obstructions and abnormalities [1].

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_17

To date, more than 2000 different CFTR mutations have been reported; the most common one, F508del, accounts for 70% of all mutations. The severity of the disease is based on the mutation class [1].

Class	Mutation defect	Specific effect of mutation class
CF classes and defects:		
I	Lack of CFTRS synthesis	No functioning CFTR chloride channels
II	Defective protein processing	CFTRS is destroyed in the cell and does not reach cell surface
III	Defective channel regulation	CFTR reaches cell surface but does not properly open for chloride transport
IV	Defective chloride conduction	CFTR function is poor and chloride conduction is defective
V	Reduced amount of CFTR protein	Decreased production of CFTR
VI	Increased turnover of CFTR at cell surface	CFTR is functional but unstable at cell surface and is removed and destroyed

Initial diagnosis of CF in children is done via the reflex sweat chloride testing. If the test is positive for CF, a conventional sweat test (through transdermal administration by iontophoresis of pilocarpine) is performed to provide a definitive diagnosis of CF. A concentration greater than 60 mmol/L is diagnostic. Repeat of chloride test is performed to verify diagnosis. Patients diagnosed with CF by sweat test and/or newborn screening and genotyping require extensive follow-up and management for the rest of their lives [1].

17.2.2 Pathophysiology

The classic presentation of CF is respiratory insufficiency or gastrointestinal (GI) disturbances in an infant [3].

CF patients are born with apparently normal lungs, followed by the acquisition of chronic bacterial infections of the airways in the first few years of life, reflecting the failure of the innate defense mechanisms of the lung against inhaled bacterial organisms [1]. The initial pathogens are usually *Staphylococcus aureus* and Hemophilus influenzae [3]. Subsequently, chronic infection with *Pseudomonas aeruginosa* becomes established in most patients. The aggressive use of antibiotics has led to the emergence of other Gram-negative bacilli, including the *Burkholderia cepacia* complex, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, and Pandoria apiospermum. The use of anaerobic cultures has shown that lower airway flora contains at least as many anaerobes as *P. aeruginosa* [3].

The intense inflammatory response combined with chronic infection leads to bronchiectasis, cor pulmonale, and death from respiratory failure unless the patient receives a lung transplant [1].

In addition to chronic infection, there are periods of acute deterioration of respiratory symptoms, termed "pulmonary exacerbations." They are common and effects include: (1) a marked adverse effect on quality of life; (2) failure to recover baseline lung function in up to one-third of exacerbations; (3) an association with accelerated deterioration in lung function; and (4) an adverse impact on prognosis. Other important respiratory complications include allergic bronchopulmonary aspergillosis, pneumothorax (which carries a bad prognosis because of associated severe lung disease), massive hemoptysis, and lung or lobar collapse [4].

Pulmonary function tests and arterial blood analysis are used to determine the severity of pulmonary exacerbations as well as disease progression; patients with declining lung function may exhibit hypoxemia and respiratory acidosis [5].

About 3% of patients will experience a spontaneous pneumothorax during their lifetime; these occur mostly in older adults with end-stage disease. Treatment depends on the size of the spontaneous pneumothorax and patient stability [3].

Pulmonary hypertension is often seen in older adults with advanced lung disease, which is associated with worse outcomes and increased mortality**.** Specific pulmonary hypertension therapy does not benefit these patients because of their advanced disease. Delaying disease progression is the best treatment for limiting pulmonary hypertension [3].

The most common comorbidity is CF-related diabetes. It occurs in 40–50% of adults and about 20% of children. Guidelines set by the Cystic Fibrosis Foundation (CFF), the Pediatric Endocrine Society (PES), and the American Diabetes Association (ADA) recommend diagnosis of a stable patient based on current ADA guidelines for diabetes. An unstable or acutely ill patient can be diagnosed with a fasting blood glucose greater than 126 mg/dL or a 2-h postprandial plasma glucose greater than 200 mg/dL, without the classic symptoms of diabetes. CF-related diabetes is due to insulin insufficiency, so the only recommended treatment is insulin therapy [1].

Common GI signs and symptoms include abdominal distension, steatorrhea, biliary cirrhosis, and volvulus or intussusception. Genitourinary signs and symptoms include undescended testes, congenital bilateral absence of the vas deferens, and decreased fertility in females. Other significant signs and symptoms are nasal polyps, bronchiectasis, pancreatic insufficiency, and sterility [4].

17.2.3 Lung Function

CF in adults can be broadly described as an obstructive lung disease, characterized by reduced FEV1 and reduced forced vital capacity. Lung volumes and compliance tend to be reduced, with increased airway resistance as a result of airway obstruction, airway inflammation, increased secretions, and parenchymal inflammation/fibrosis. Gas transfer is typically preserved until late in the disease, consistent with radiological and histopathological observations of preserved alveolar integrity [5].

FEV1 is not used for diagnosis but is the major monitoring tool of disease progression and is the primary measurement used to grade the severity of CF lung disease – with FEV1 between 80% and 60% traditionally representing mild impairment, 40% and 60% moderate impairment, and < 40% severe impairment [5].

FEV1 is also used to identify an exacerbation, typically regarded as a fall in FEV1 > 10% with accompanying clinical symptoms. It also features in evaluations of response to new therapies and in decisions about when to refer for lung transplant [5].

Low FEV1 has been correlated with reduced PaO_2, increased $PaCO_2$, reduced lung compliance and increased respiratory load. In severe CF, increased load from airflow obstruction (detected by FEV1) and reduced capacity from respiratory muscle fatigue may contribute to hypercapnia [6].

Lung clearance index (LCI) is derived from the cumulative expired volume required to wash out tracer, divided by the functional residual capacity (FRC). Improved sensitivity and therapeutic responsiveness of LCI mean that it has a particular role in those with milder disease. LCI is sensitive to alterations in airway physiology throughout the airway tree, including very peripheral airway effects and this probably accounts for its particular sensitivity in early CF. In CF adults, abnormalities in LCI appear to be caused by both increased dead space and increased specific ventilation heterogeneity. The potential for LCI in pediatrics is increasingly recognized but is much less well appreciated in adults who tend to have more advanced airway dysfunction [5].

Forced oscillation techniques (FOT) involve delivery of a waveform to the airway (usually at the mouth) using a loudspeaker. This creates pressure oscillations that are used to perturb the respiratory gas column, airway, lung parenchyma, and chest wall, and generate a corresponding flow. Heterogeneous small airways obstruction can be detected using FOT systems, particularly at low frequencies. The role of FOT remains poorly understood, but recent advances may support greater application of this relatively quick and noninvasive technique using commercial variants such as IOS and handheld portable sinusoidal FOT devices [5].

Reduced exercise capacity is common in CF, and the mechanisms differ depending on severity of lung disease. The primary mechanisms of reduced exercise performance in CF are ventilatory, as in other severe respiratory diseases [5].

Cardiopulmonary exercise testing (CPET) provides useful information across the full spectrum of disease severity, but its role also changes with disease severity from one of supporting exercise in those with milder disease to prognostication and rehab [5].

Recent developments in understanding the physiological impact of CF on lung function come from advances in hyperpolarized gas magnetic resonance imaging. This allows direct visualization of the distribution of a single breath of hyperpolarized tracer gas and construction of high-resolution three-dimensional maps of ventilation distribution. This shows that ventilation defects broadly correlate with structural abnormalities. Gas distribution appears to be affected by a combination of fixed structural defects, reversible airway inflammation, and mobile mucus secretions; and it is these latter two components that may be amenable to intervention [5].

17.2.4 Noninvasive Ventilation in Cystic Fibrosis

NIV may be a means to temporarily reverse or slow the progression of respiratory failure in cystic fibrosis by providing ventilatory support and avoiding tracheal intubation. Using NIV can improve lung mechanics through increasing airflow and gas exchange and decreasing the work of breathing. NIV, thus, acts as an external respiratory muscle [6].

NIV may be a useful adjunct to other airway clearance techniques, particularly in people with CF who have difficulty expectorating sputum or where fatigue or respiratory muscle weakness is an issue. It can also benefit patients with CF who experience daytime hypercapnia in terms of exercise tolerance, dyspnea, and nocturnal gas exchange. When used together with overnight oxygen, NIV improves gas exchange during sleep to a greater extent than oxygen therapy alone in people with moderate-to-severe CF [6].

The impact of this therapy on pulmonary exacerbations and disease progression remain unclear. There is one trial of a single session of NIV that increased functional capacity in children with stable disease [6].

In CF, NIV can be a bridge to lung transplantation. NIV is often continued during end of life with many patients on treatment until death [6].

Pneumothorax and hemoptysis, often considered contraindication to NIV, should not limit the use of this technique [6].

17.3 Conclusion Discussion

CF is a life-threatening genetic disorder that causes multiorgan system disease. Its effects on the pulmonary system are the leading cause of patient morbidity and mortality.

Advancements in the diagnosis and management of CF provided significant improvements in early diagnosis and delayed disease progression. The patient survival rate is increasing and supportive treatment is becoming more widely available.

In severe CF with respiratory insufficiency, NIV can be a bridge to lung transplantation and is often continued during end of life.

Addressing the genetic mutation ultimately will reduce the treatment burden on patients and provide a higher-quality life with greater survival. Drugs are being developed to target and correct the misprocessing of the CFTR protein.

Key Major Recommendations

- CF is a life-threatening genetic disorder caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene; it, thus, causes an accumulation of thick and viscous mucus secretions in various organ systems; and its effects on the pulmonary system are the leading cause of patient morbidity and mortality.
- CF is an obstructive lung disease, characterized by reduced FEV1 and reduced forced vital capacity. Lung volumes and compliance tend to be reduced, with increased airway resistance as a result of airway obstruction, airway inflammation, increased secretions, and parenchymal inflammation/fibrosis. Gas transfer is typically preserved until late in the disease.
- Using NIV can improve lung mechanics through increasing airflow and gas exchange and decreasing the work of breathing.

- In severe CF with respiratory insufficiency, NIV can be a bridge to lung transplantation and is often continued during end of life.

References

1. Brown SD, White R, Tobin P. Keep them breathing: cystic fibrosis pathophysiology, diagnosis, and treatment. J Am Acad Phys Assist. 2017;30:24–7.
2. Marini JJ. Dynamic hyperinflation and pulmonary inflammation: a potentially relevant relationship? Am J Respir Crit Care Med. 2011;184:756–62.
3. Horsley AR, Davies JC, Gray RD, et al. Changes in physiological, functional and structural markers of cystic fibrosis lung disease with treatment of a pulmonary exacerbation. Thorax. 2013;68:532–9.
4. Boucher RC. New concepts of the pathogenesis of cystic fibrosis lung disease. Eur Respir J. 2004;23:146–58.
5. Horsley A, Siddiqui S. Putting lung function and physiology into perspective: cystic fibrosis in adults. Respirology. 2015;20:33–45.
6. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. Cochrane Database Syst Rev. 2017;2:CD002769.

18 Should NPPV be Used for Respiratory Management of Asthma Attacks?

Yoshinori Matsuoka, Kei Kurihara, Yoshitaka Nishiyama, and Takuma Sakai

Abstract

Noninvasive positive pressure ventilation (NPPV) may be attempted for treatment of acute respiratory failure during asthma attacks. However, it is necessary to shift to respiratory management under tracheal intubation without hesitation if the asthma attack worsens rapidly. There is currently insufficient evidence that NPPV is effective for severe asthma attacks according to previous RCT studies.

Keywords

Asthma · Mechanical ventilation · Noninvasive ventilation · Severe asthma attacks · Noninvasive positive pressure ventilation

Abbreviations

ACOS	Asthma and COPD overlap syndrome
CPAP	Continuous positive airway pressure
EPAP	End positive airway pressure
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IPAP	Inspiratory positive pressure
IPPV	Intermittent positive pressure ventilation
NPPV	Noninvasive positive pressure ventilation

Y. Matsuoka (✉) · K. Kurihara · Y. Nishiyama
T. Sakai
Wide Area Medical Corporation EMS, Fukuoka, Japan

18.1 Introduction

It has been estimated that there are approximately 300 million patients with bronchial asthma worldwide, and a prevalence rate of 3–6% of the total population has been reported in Japan. More than 30% of patients will be poorly controlled even if the treatment recommended by the current guidelines is implemented, and the impact on society is not small. On the other hand, regarding chronic obstructive pulmonary disease (COPD), its prevalence over the age of 40 in 12 regions around the world is approximately 10% of the total. The World Health Organization predicts that COPD will be the third leading cause of death among all diseases by 2020.

Asthma and COPD have different pathological conditions due to different causes and mechanisms, and the pathological conditions of airway inflammation and airflow obstruction are also different. However, it has long been known that there are pathological conditions with both characteristics. It was common in previous studies and clinical trials on asthma and COPD to clearly

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_18

distinguish these diseases and exclude cases in which they were combined. However, it was often difficult to clearly distinguish between asthma and COPD in clinical practice.

GINA (Global Initiative for Asthma) and GOLD (Global Initiative for Chronic Obstructive Lung Disease), the international debate committee for asthma and COPD, jointly proposed to deal with this situation in 2015. "Asthma and COPD Overlap Syndrome (ACOS)" was the prototype of ACO.

The term "syndrome" was considered inappropriate for a variety of reasons, in subsequent discussions, and "Asthma and COPD Overlap (ACO)" was proposed. This defined the name "ACO" and made it easier to understand as one of the clinically common pathological conditions of obstructive lung disease.

It will not be necessary to clearly distinguish between asthma and COPD in the future, and it may be possible to move toward diagnosis and treatment as ACO.

The death toll from severe asthma attacks remains high and is a serious problem in respiratory emergencies. Inhalation and oxygen administration of short-acting bronchodilators (β2 stimulants), intravenous steroid injection, subcutaneous epinephrine injection in severe cases, and artificial respiration therapy are the basics of asthma treatment in the emergency area. Especially for artificial respiration, noninvasive positive pressure ventilation (NPPV) has recently been performed [1–3].

Many studies have been conducted on the exacerbation of COPD, regarding NPPV in acute respiratory failure, and it is recognized as a well-founded treatment [4]. The concept of NPPV is that the pathophysiology of asthma attacks is in many ways similar to the exacerbation of COPD. Furthermore, patients with respiratory failure due to an asthma attack recover quickly when the attack is relieved, so the time for artificial respiration may be shortened [1].

The first choice of treatment for severe asthma attacks is inhalation or injection of β-2 stimulants, systemic administration of steroids, and oxygen inhalation according to GINA, which is the global guideline for asthma. ICU admission, tracheal intubation, and mechanical ventilation therapy could be considered for patients with poor response to these treatments.

There are no descriptions of NPPV, and its effect is not clear even in other NPPV-related guidelines.

Mechanical ventilation by tracheal intubation is currently considered as the first-line mechanical ventilation therapy for asthma attacks, but NPPV is also a treatment method whose usefulness is being investigated. Asthma guidelines in Japan indicate that NPPV may improve a patient's respiratory pattern by maintaining airway patency at the end of exhalation with pressure assistance and PEEP. However, treatment by an experienced specialist is desirable, if attempted. Moreover, it is stated that patients with impaired consciousness and patients with high airway secretions should be careful not to delay the start of tracheal intubation and mechanical ventilation management [5]. This leads us to question whether NPPV is effective for asthma.

18.2 Discussion and Analysis of the Main Topic

In 1982, Martin et al. reported that the addition of CPAP dilates the airway, reduces airway resistance, and reduces respiratory work in histamine-induced asthma attacks [5].

Shivaram et al. reported that nasal CPAP improves respiratory rate and dyspnea in asthma attacks without adversely affecting the hemodynamics [6].

Then, Meduri et al. compared the efficacy of NPPV and IPPV in patients with severe asthma attacks who were admitted to the ICU, in 1996. NPPV corrected respiratory acidosis in patients with asthma attacks, and intubation occurred in only 2 of 17 patients, which was similar to IPPV. The NPPV group had significantly lower airway pressure and no complications [1].

Fernandez et al. conducted a comparative study of NPPV and IPPV for asthma attacks in the emergency room in a retrospective study. $PaCO_2$ decreased, pH improved, and intubation avoidance was 67% (22/33) in the NPPV

group. However, they reported that there were no significant differences in length of stay in the ICU, length of hospital stay, or prognosis [2]. In Japan, Murase et al. conducted a retrospective study comparing fatal asthma attacks before and after the introduction of NPPV. They determined that it significantly reduced the intubation rate after introduction of NPPV (2/57 (3.5%) vs. 9/50 (18%), $p = 0.01$) and shortened hospital stay (8.4 ± 2.8 vs. 12.6 ± 4.2 days, $p < 0.01$) [7]. Holley et al. examined the efficacy of NPPV in a randomized controlled trial and reported that intubation rate, length of hospital stay, and cost of hospitalization tended to decrease even though there was no significant difference. In this investigation, the clinical trial was terminated prematurely due to ethical concerns about not using NPPV3.

In a randomized controlled trial, Soroksky et al. examined the efficacy of NPPV in 30 patients with severe asthma attacks who visited the emergency department [8]. As a result, it was reported that the use of NPPV for 3 h significantly improved lung function and prevented hospitalization compared to the control group. Soma et al. examined the efficacy of NPPV in combination with inhalation therapy in the emergency department. In a study divided into IPAP/EPAP 8/6 cmH_2O group, 6/4 cmH_2O group, and control group, FEV1.0 was significantly improved in the 8/6 cmH_2O group, and dyspnea and wheezing were improved in the NPPV group [9]. Brandao et al. examined the effect of 15-min inhalation therapy with NPPV in the emergency department. Peak flow, FEV1, and FVC were improved in the 15/10 cmH_2O group [10] compared to the IPAP/EPAP 15/5 cmH_2O group, 15/10 cmH_2O group, and control group.

Gupta et al. conducted a comparative study of NPPV therapy with IPAP/EPAP 12/5 cmH_2O and a control group in 53 patients. There were no significant differences in intubation rate, but NPPV reduced the total length of hospital stay, length of stay in the ICU, and total amount of bronchodilators used [11]. Galindo-Filho et al. found improvements in respiratory rate, tidal volume, expiratory volume, peak flow, FEV1, FVC, IC, and inhalation efficiency after 9 min of inhalation therapy with IPAP/EPAP 12/5 cmH_2O [12].

The combined use of NPPV and inhalation therapy is expected to improve inhalation efficiency and lung function in patients with asthma attacks, based on the above results of RCT studies worldwide, but the effect of avoiding intubation is not clear. Therefore, it is concluded that there is insufficient evidence that NPPV is effective for severe attacks of asthma.

18.3 Conclusion Discussion

On the other hand, a national survey in the United States between 2000 and 2008 showed that the proportion of invasive artificial respiration management decreased, while the proportion of NPPV increased, in artificial respiration management for acute asthma attacks in clinical practice. The indications in clinical practice are being expanded.

(1) Decreasing airway resistance by applying positive pressure by CPAP/EPAP on the airway (for endogenous PEEP), (2) assisting ventilation by pressure support if ventilation is inadequate, and (3) avoiding intubation have been considered as the advantages of NPPV for asthma attacks. Complications associated with intubation can be avoided by avoiding tracheal intubation, in particular, and artificial ventilation can be started promptly. Furthermore, there is no concern about bronchospasm due to the tracheal tube, and there is the advantage that oral intake and oral treatment can be continued. GINA has shown a rapid improvement in respiratory function with the combined use of NPPV, and it is expected that the introduction of NPPV at an earlier stage than the purpose of avoiding intubation is expected.

18.3.1 Criteria for Introducing NPPV in Asthma

The criteria for adaptation of NPPV for asthma attacks have not been clearly examined so far. The introduction standards of GINA and Japan's NPPV are tentatively shown in Table 18.1. The point is that it may be introduced early for patients whose conditions, such as tachypnea and

Table 18.1 Indications for NPPV during bronchial asthma attacks

1. Dyspnea with poor improvement by inhalation of β2 agonist
2. Significant labored breathing
3. Obvious respiratory muscle exhaustion
4. $PaCO_2$ rise ($PaCO_2 > 45$ mmHg)

Table 18.2 Criteria for mechanical ventilation through tracheal intubation in asthma attacks

1. Respiratory arrest
2. Disturbance of consciousness
3. Obvious respiratory muscle exhaustion
4. Rapid increase in $PaCO_2$ ($PaCO_2 > 60$ mmHg or 5 mmHg or more per hour)
5. $PaO_2 < 50$ mmHg under maximum oxygen administration

respiratory acidosis, do not improve and that we do not significantly adhere to NPPV when the response to NPPV is poor. It is important to recognize that NPPV is not substitute for intubation management. Needless to say, drug therapy is also performed in parallel with respiratory management. It is desirable to use an NPPV-dedicated device that can regulate the inhaled oxygen concentration even for asthma attacks, since many cases of acute respiratory failure are complicated by hypoxemia.

18.3.2 Initial Settings for NPPV

The following method is presented for the initial setting and subsequent management of NPPV for asthma. Start with IPAP 8 cmH_2O and EPAP 4 cmH_2O and increase IPAP and EPAP at bedside according to the patient's respiratory rate, respiratory pattern and auscultatory findings, and dyspnea (assessed on the Borg scale). Furthermore, endogenous PEEP may be released and subjective symptoms may be improved, even in CPAP mode alone. You should be prepared to move to tracheal intubation immediately if there are signs of exacerbation in either case.

18.3.3 Monitoring while Using NPPV

Strict continuous or intermittent measurement of electrocardiogram, blood pressure, and SpO_2 is conducted during NPPV. Evaluate breath sounds and dyspnea. Blood gas is also measured every 30 min for approximately 2 h after starting to check for the progress of respiratory acidosis. Until the patient is stabilized, blood gas is checked when changing settings for every few hours. Pay attention to the level of consciousness and consider the transition to tracheal intubation even when the level of consciousness decreases or the disorder of consciousness persists.

18.3.4 Indications for Tracheal Intubation

The indications for tracheal intubation are shown in Table 18.2. Tracheal intubation should be managed from the beginning if there is respiratory arrest or impaired consciousness. Intubation is indicated when respiratory muscle exhaustion, rapid increase in $PaCO_2$, or hypoxemia is observed even after NPPV. Furthermore, patients with $PaCO_2$ of 45 mmHg or higher should be prepared to switch to artificial respiration by intubation at any time because asthma attacks may worsen rapidly.

18.3.5 NPPV Withdrawal Criteria

It is necessary to provide sufficient explanation of the treatment, relaxation, and positioning when performing NPPV, in order to eliminate patient anxiety. Physiotherapy approaches, such as breathing instruction, respiratory assistance, and removal of airway secretions, are important to maximize the effects of NPPV in severe cases. Oral intake should be started if the respiratory condition is improved by inhalation therapy or steroid treatment, but NPPV should be reattached immediately if NPPV is removed and dyspnea worsens. When determining the timing of NPPV withdrawal, it is useful to check vital signs, SpO_2, blood gas, etc. if NPPV is temporarily removed, such as during meals and breaks. Turn off NPPV,

observe the progress with oxygen inhalation only, and check vital signs and blood gas again several hours later if subjective/objective symptoms, such as wheezing and dyspnea, have improved and respiratory acidosis has disappeared. Then, it is judged whether it can be detached as it is or whether the NPPV must be attached again.

Although reports suggesting its effectiveness are being accumulated, there is still no clear evidence of the usefulness of NPPV for asthma attacks. Respiratory function can be improved faster, dyspnea and hypercapnia can be improved, tracheal intubation can be avoided, and inhalation therapy can be performed efficiently if the indications are examined and performed in a facility that is fully proficient in NPPV3. On the other hand, asthma attacks may worsen rapidly and may be life-threatening if the timing of intubation is delayed. Therefore, it is necessary to shift to respiratory management under tracheal intubation without hesitation if there are signs of exacerbation.

Key Major Recommendations

- NPPV may be attempted for acute respiratory failure due to asthma attacks.
- It is necessary to shift to respiratory management under tracheal intubation without hesitation if the asthma attack worsens rapidly.

References

1. Meduri GU, Cook TR, Turner RE, et al. Noninvasive positive pressure ventilation in status asthmatics. Chest. 1996;110:767–74.
2. Fernandez MM, Villagra A, Blanch L, et al. Noninvasive mechanical ventilation in status asthmatics. Intensive Care Med. 2001;27:486–92.
3. Holley MT, Morrissey TK, Seaberg DC, et al. Ethical dilemmas in a randomized trial of asthma treatment: can Bayesian statistical analysis explain the results? Acad Emerg Med. 2001;8:1128–35.
4. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary: global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 163:1256–1276.
5. Martin JG, Shore SA, Engel LA. Mechanical load and inspiratory muscle action during induced asthma. Am Rev Respir Dis. 1983;128:455–60.
6. Shivaram U, Miro AM, Cash ME, et al. Cardiopulmonary responses to continuous positive airway pressure in acute asthma. J Crit Care. 1993;8:87–92.
7. Murase K, Tomii K, Chin K, et al. The use of noninvasive ventilation for life-threatening asthma attacks: changes in the need for intubation. Respirology. 2010;15:714–20.
8. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive air- way pressure in acute asthmatic attack. Chest. 2003;123:1018–25.
9. Soma T, Hino M, Kida K, et al. A prospective and randomized study for improvement of acute asthma by non-invasive positive pressure ventilation (NPPV). Intern Med. 2008;47:493–501.
10. Brandao DC, Lima VM, Filho VG, et al. Reversal of bronchial obstruction with bi-level positive airway pressure and nebulization in patients with acute asthma. J Asthma. 2009;46:356–61.
11. Gupta D, Nath A, Agarwal R, et al. A prospective randomized controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. Respir Care. 2010;55:536–43.
12. Filho VC, Brandao DC, Ferreira R de CS, et al. Noninvasive ventilation coupled with nebulization during asthma crises: a randomized controlled trial. Respir Care. 2013;58:241–9.

19 Pulmonary Function Measurement in Noninvasive Ventilatory Support: Obesity Hypoventilation Syndrome

Mediha Turktan

Abstract

Obesity hypoventilation syndrome is a clinical condition characterized by the association of alveolar hypoventilation, hypercapnia, and daytime sleepiness in obese patients without any other causes of chronic hypercapnia. The most effective method in treatment is positive pressure ventilation including noninvasive ventilation and continuous positive airway pressure. Close monitoring of the patients' pulmonary function is important for the effectiveness of treatment.

Keywords

Continuous positive airway pressure · Noninvasive ventilation · Obesity hypoventilation syndrome · Pulmonary function

Abbreviations

AHI	Apnea hypopnea index
BMI	Body mass index
BPAP	Bilevel positive airway pressure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory component
FEV_1	Forced expiratory volume in 1 s
IPAP	Inspiratory component
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PEEP	Positive end-expiratory pressure
V_tPS	Volume-targeted pressure support

M. Turktan (✉)
Anesthesiology Department, Cukurova University Faculty of Medicine, Adana, Turkey

19.1 Introduction

Obesity hypoventilation syndrome (OHS) is defined by hypoventilation, chronic awake hypercapnia ($PaCO_2$ > 45 mmHg, at sea level), and excessive daytime sleepiness in patients with body mass index (BMI) upper than 30 kg/m^2 without any other neurological, muscular, mechanical, or metabolic cause for chronic hypercapnia. There is a strong correlation between BMI and prevalence of OHS.

The most common symptoms of OHS are snoring, daytime sleepiness, fatigue, witnessed apnea, morning headaches, and night choking sensation [1]. The most common morbidities in the patients with OHS are cardiovascular diseases such as congestive heart failure, angina pectoris, and cor pulmonale. The patients with OHS have a longer hospital stay; they need intensive care more than the normal population and

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_19

even obese patients without OHS. Consequently, OHS leads to increase in health expenditures and decrease in quality of life and quality of sleep.

19.2 Discussion and Analysis of the Main Topic

19.2.1 Pathophysiology

Although the pathophysiology of OHS is not fully clear, inappropriate response to hypoxemia and hypercapnia and changes in neurohumoral response and lung mechanics may play a role. In obese patients, chest wall thickness and upper airway resistance increase, functional residual capacity decreases, respiratory muscle performance is impaired, and all of them cause to increase the work of breathing. The patients have lower tidal volume and higher respiratory rate due to worsening of the ventilation/perfusion ratio and hypoxemia. Abnormally low lung volumes led to reduced chest wall and respiratory system compliance. If the expiratory reserve volume becomes too low, small airways close and intrinsic positive end-expiratory pressure (PEEP) occurs. This condition is more pronounced in the obese patients with supine position. Increased intraabdominal pressure not only worsens the work of breathing but also increases oxidative stress [2]. Prolonged hypercapnia also impairs central chemoreceptor ventilator response. Apnea and hypopnea attacks occurring throughout the day aggravate existing hypercapnia. Elevated bicarbonate levels may also contribute to affect chemosensitivity [1]. In mice, leptin deficiency associated with respiratory depression, abnormal respiratory muscle function, awake hypercapnia, and leptin replacement acts as a respiratory stimulant [3].

On the contrary, in humans, leptin resistance or central leptin deficiency develops with obesity over time, and it causes a decrease in ventilator response [3]. In addition, a strong negative correlation between growth factor and both levels of $PaCO_2$ and bicarbonate has been reported [3].

19.2.2 Diagnostic Tests

The diagnosis and treatment of OHS is very critical because of high prevalence and high morbidity-mortality in untreated patients. Other factors that cause hypoventilation should be excluded. The most common diseases confused in morbid obese patients with OHS are chronic obstructive pulmonary disease (COPD) and congestive heart failure. Therefore, arterial blood gas analysis, pulmonary function tests, chest X-ray, electrocardiography, and function of respiratory muscles should be evaluated. Detailed physical examination and anamnesis are substantial.

The most common finding in biochemical tests are hypoxemia and secondary polycythemia. For hypoventilation, $PaO_2 < 70$ mmHg or $SpO_2 < 94\%$ may be a warning, but higher values for both parameters do not exclude OHS [1]. In arterial blood gas analysis, an increase in HCO_3 level due to respiratory acidosis is common. Mokhlesi and colleagues reported that serum bicarbonate level greater than 27 mEq/L had 92% sensitivity and 50% specificity for OHS [2]. According to a retrospective analysis of Macavei et al., calculated bicarbonate levels have a sensitivity of 85.7% and specificity of 89.5% for OHS [4]. In addition, calculated base excess above 2 mmol/L is one of the frequently encountered findings. These cut-off values are still controversial, but elevated bicarbonate level should alert the clinician in terms of OHS.

The most obvious finding in polysomnography is severe long-term desaturation. However, polysomnography is not necessary for diagnosis of OHS, because OHS and obstructive sleep apnea (OSA) may not always coexist [1]. The lowest oxygen value <60 mmHg during sleep at night and high apnea hypopnea index (AHI) are shown to be valuable for diagnosis of OHS [3].

Right heart failure findings are common as a result of chronic hypoxemia and pulmonary hypertension. Intercalarily, arterial hypertension, and insulin resistance are more common in patients with OHS than in obese individuals without OHS [1].

19.2.3 Treatment

The purposes of therapy in OHS include restoring $PaCO_2$ value, normalizing nocturnal breathing and gas exchange, preventing desaturation during a day, correcting acid-base balance, preventing the formation of cor pulmonale by correcting oxyhemoglobin level, reducing body weight, relief of hypersomnia, and increasing life quality. Therefore, the treatment is multifactorial and the adherence of the patients to treatment is very important.

Lifestyle change (weight loss, increased physical activity) is the initial step for the treatment of OHS and may help to improve the ventilation parameters. Bariatric surgery and low-calorie diet may be applied, but some patients are not suitable for surgery due to their comorbidities. Moreover, the patients should continue to be followed closely after bariatric surgery procedure. Despite faster weight loss in a shorter time with bariatric surgery, no difference was found between the two methods (conventional or surgical) in terms of AHI. Weight loss or low-calorie diet alone has not been shown to significantly improve nocturnal gas exchange, AHI, clinical symptoms, or awake hypercarbia [5].

Tracheostomy was one of the most frequently used methods in the past, but today, it is only considered in patients resistant to noninvasive ventilation due to current risks. It may not be chosen as a long-term treatment option.

One of the points to be considered in treatment is to avoid excessive oxygen use.

Increased FiO_2 decreases minute volume and tidal volume, increases dead space due to vasodilation in poorly ventilated areas, causes inability to correct hypoxia with Haldane effect [1].

For these reasons, oxygen therapy alone is not recommended in hemodynamically stable patients without extreme respiratory distress, and it should be administered under clinical observation with target SpO_2 range of 89–92%. Nocturnal oxygen therapy does not reduce hypercarbia and clinical symptoms.

Short-term respiratory stimulants (medroxyprogesterone, acetazolamide, etc.) are not recommended for the treatment of OHS [1].

Loop diuretics may be added to medical treatment in the patients with cor pulmonale. It is recommended to start with a lowest possible dose in order to prevent acute prerenal renal failure and hypokalemia that may occur in overuse. Depending on the use of diuretics developed metabolic alkalosis may worsen CO_2 retention.

Phlebotomy can be applied in patients with hematocrit <56% and hyperviscosity symptoms, but the effect on treatment of OHS has not been proven yet [1].

Positive airway pressure (PAP) ventilation strategies including continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) are the cornerstone therapy in patients with OHS. They decrease upper airway pressure, remove upper airway obstruction, increase central respiratory activity, eliminate repetitive obstructive events, and improve alveolar hypoventilation. In addition, quality of life and sleep quality are improved. Early initiation of PAP therapy may prevent the need for invasive mechanical ventilation. The effect of PAP on cardiovascular complication and mortality in the patients with OHS is limited, so it is recommended to be combined with lifestyle changes (weight loss and increased physical activity) [5].

Improvements in daytime gas exchange and symptoms have been shown with both CPAP and NIV. NIV is thought to be more effective than CPAP on physiological disturbances in OHS. However, there is no convincing evidence including NIV therapy is superior to CPAP therapy in the patients with OHS. For all that, in both therapy modalities (NIV and CPAP), clinical symptoms, nocturnal gas exchange awake hypercapnia, and sleep quality are better than lifestyle modification [1]. There is no differences between CPAP and NIV in terms of treatment failure, quality of life, patient safety, cardiovascular risks, clinical symptoms, bicarbonate levels, and $PaCO_2$ after 2 months of interventions [6, 7]. However, NIV therapy improves forced expiratory volume in 1 s (FEV_1), quality of life, and functional capacity (6-min walk distance) more than CPAP therapy [7]. Corral et al. demonstrated that NIV is more effective than CPAP in improving measures of systolic pulmonary artery pres-

sure and left ventricle hypertrophy in the patients with OHS [8]. In addition, CPAP reduces neural respiratory drive in obese patients, but it may be insufficient to overcome the work of breathing caused by obesity-induced reductions in chest wall compliance [9].

If the patient is clinically stable and $PaCO_2$ levels are acceptable (<55 mmHg), CPAP should be preferred as initial therapy for positive pressure ventilation. The least costly and simplest therapy of all PAP treatment is CPAP, and it may be also considered after stabilization of hypercapnia with BPAP. Nasal mask application is often preferred due to higher patient compliance and efficiency, but in critically ill patients with respiratory failure, oronasal masks are recommended [1]. In most cases, upper airway obstruction can be removed with nasal CPAP and nocturnal hypercarbia is prevented [3]. CPAP therapy increases functional residual capacity and prevents small airway closure and this way helps to normalize breathing during sleep and improve nocturnal gas exchange [5]. Especially, the patients with high AHI benefit from nocturnal CPAP therapy and pressure support up to 10–16 cmH_2O is generally required [10]. Manuel titration of CPAP is recommended instead of autotitration CPAP, and the patient should be closely monitored especially during the first month of therapy. The most important parameters affecting the success of CPAP therapy at 3 months are mean nocturnal oxygen saturation during the first night and daytime $PaCO_2$ levels at 1 month [11]. Despite its positive effects, CPAP does not provide additional ventilatory support.

In the patients with persistent hypercarbia ($PaCO_2 > 45$ mmHg) and persistent desaturation ($SpO_2 < 90\%$) during CPAP treatment despite the treatment by titration of pressure and elimination of obstructive events, NIV should be started [1]. Noninvasive ventilation can be applied basically with volume- or pressure-targeted mode. In volume-targeted mode, the tidal volume and flow velocity are determined by the clinician, but IPAP (inspiratory positive airway pressure) varies depending on airway resistance. In pressure-targeted mode, conversely, the tidal volume is created by reaching a predetermined IPAP. Although pressure-targeted NIV is more easily tolerated, more stable tidal volumes are provided with volume-targeted NIV.

The most commonly used NIV mode is bilevel positive airway pressure (BPAP). This mode provides increased tidal volume through the inspiratory component (IPAP) in addition to the expiratory component (EPAP) providing the same effects as CPAP therapy [10]. Although there is still no consensus on how best to titrate BPAP, pressure support (IPAP-EPAP) is recommended to be at least 4 cmH_20 (6–7 cmH_20, according to some published studies) and initial EPAP 4–6 cmH_20 to effectively improved ventilation [3, 10]. BPAP has spontaneous (S) and spontaneous-timed (ST) modes, and both are used in the patients with OHS. The advantage of BPAP mode over CPAP mode is that BPAP not only keeps the upper airway open but also provides active ventilation. However, patient ventilator incompatibility, which is not common in CPAP therapy, is more common in BPAP therapy especially in ST mode [5]. Variability of delivered tidal volume due to respiratory effort, respiratory system compliance, and changes in sleep position is the another disadvantage of BPAP [10]. Therefore, BPAP with volume-targeted pressure support (V_tPS) or BPAP-ST mode may be a more suitable mode in this patient group. Thus, the addition of V_tPS provides higher tidal volume and minute ventilation, a significantly greater reduction in nocturnal hypercapnia [10]. BPAP therapy significantly decreases $PaCO_2$ and AHI, increases PaO_2, and improves sleep structure in the patients with OHS. Additionally, it offers fewer hospitalization and better quality of life to the patients. Since BPAP therapy is pressure sensitive, if the patient has upper airway obstruction or the respiratory system compliance is low, the tidal volume formed when the set pressure is reached may remain low and it may result in hypoventilation. Therefore, in case of severe upper airway obstruction, both EPAP and IPAP should be increased together in BPAP mode or volume-targeted pressure support should be used.

Standard NIV modes may not be able to maintain adequate ventilation during the changes in pulmonary mechanics. In recent years, hybrid

modes have been used in NIV treatment, and these modes may offer potential advantages, especially in obese patients [12]. The most studied hybrid mode is average volume-assured pressure support (AVAPS) mode, and it provides a more constant tidal volume in addition to the tolerability of pressure support ventilation. In this sense, AVAPS may be considered as a subtype of V_tPS mode. In AVAPS mode, automatically adjusted pressure support (IPAP) varies between minimum and maximum values ($IPAP_{min}$ and $IPAP_{max}$). The clinicians set up tidal volume according to ideal body weight (7–10 mL/kg), EPAP (4–6 cmH_20), $IPAP_{min}$ (=EPAP), $IPAP_{max}$ (20–25 cmH_2O, in obese patients max 30 cmH_20), and respiratory rate (12/min).

With AVAPS mode, nocturnal and daytime hypercapnia significantly decreases compared to initial values and the use of BIPAP-ST alone [13]. In the patients with chronic respiratory failure, higher minute ventilation values were obtained during the sleep with AVAPS mode compared to pressure-targeted NIV, but PaO_2 and $PaCO_2$ levels in the arterial blood gas analysis, O_2 saturation values were found to be similar with both modes [13].

19.3 Conclusion Discussion

In fact, regardless of the mode chosen, failure to control upper airway obstruction causes persistent desaturation. Sufficient EPAP must be applied to prevent this condition [5]. The advantages of pressure-targeted and volume-targeted modes to each other are not clear in the patients with OHS, but similar tidal volumes (7–10 mL/ideal body weight) should be applied in both modes. More than 4 hours nocturnal NIV is required to achieve a reduction in daytime carbon dioxide, and nocturnal ventilatory support improves daytime symptoms and physical activity in this patient group [12]. The increased physical activity may contribute to weight loss, reducing clinical symptoms and cardiopulmonary risks. During PAP therapy, vital signs, oxygen saturation, blood gas analysis, tidal volume, and consciousness of the patients should be closely monitored.

Key Major Recommendation

- Obesity hypoventilation syndrome is characterized by alveolar hypoventilation, hypercapnia, and daytime sleepiness in obese patients.
- Other causes of hypercapnia should be excluded for diagnosis.
- The most effective treatment is positive pressure ventilation combined with lifestyle change.
- The patient adherence to treatment is extremely important.
- Pulmonary function of the patients should be monitored closely during the therapy.

References

1. Athayde RAB, Filho JRBO, Filho GL, et al. Obesity hypoventilation syndrome: a current review. J Bras Pneumol. 2018;44:510–8.
2. Mokhlesi B, Tulaimat A, Faibussowitsch I, et al. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breathing. 2007;11:117–24.
3. Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. Am J Respir Crit Care Med. 2011;183:292–8.
4. Macavei VM, Spurling KJ, Loft J, et al. Diagnostic predictors of obesity-hypoventilation syndrome in patients suspected of having sleep disordered breathing. J Clin Sleep Med. 2013;9:879–84.
5. Piper A. Obesity hypoventilation syndrome: weighing in on therapy options. Chest. 2016;149:856–68.
6. Howard ME, Piper AJ, Stevens B, et al. A randomised controlled trial of CPAP vs non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017;72:437–44.
7. Masa JF, Corral J, Alonso ML, et al. Efficacy of different treatment alternatives for obesity hypoventilation syndrome: Pickwick study. Am J Respir Crit Care Med. 2015;192:86–95.
8. Corral J, Mogollon MV, Sanchez-Quiroga MA, et al. Echocardiographic changes with noninvasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax. 2018;73:361–8.
9. Steier J, Jolley CJ, Seymour J, et al. Neural respiratory drive in obesity. Thorax. 2009;64:719–25.
10. Piper AJ, BaHammam AS, Javaheri S. Obesity hypoventilation syndrome: choosing the appropriate treatment of a heterogeneous disorder. Sleep Med Clin. 2017;12:587–96.

11. Salord N, Mayos M, Miralda RM, et al. Continuous positive airway pressure in clinically stable patients with mild-to-moderate obesity hypoventilation syndrome and obstructive sleep apnoea. Respirology. 2013;18:1135–42.
12. Murphy PB, Davidson C, Hind MD, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax. 2012;67:727–34.
13. Storre JH, Seuthe B, Fiechter R, et al. Average volume assured pressure support in obesity hypoventilation: a randomized crossover trial. Chest. 2006;130:815–21.

Obstructive Sleep Apnea. Sleep-Disordered Breathing

20

Mariana Cabral, Bruno Mendes, Carlos Figueiredo, and Inês Moreira

Abstract

Breathing is an essential and dynamic process involving complex neural and physiological mechanisms. There is a difference between the breathing pattern while awake and asleep and the onset of sleep provides some important physiological changes in the organism. Therefore sleep is a period of great vulnerability to ventilation irregularities and the presence of respiratory disorders during sleep is very common, even in healthy individuals. However, the mechanism that leads to these irregularities are poorly understood.

There are a number of pathologies related to these changes in breathing pattern during sleep. One such example is OSAS, a very prevalent disease worldwide. However, there are others, namely in patients with neuromuscular disease and obesity hypoventilation syndrome, which will be discussed in this chapter.

Keywords

Sleep breathing disorder · Hypoventilation · Apnea · Neuromuscular disease

Abbreviations

AHI	Apnea/hypopnea index
BMI	Body mass index
CSA	Central sleep apnea
ERV	End expiratory volume
FEV1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
FVC	Forced vital capacity
NIV	Noninvasive ventilation
NMD	Neuromuscular disease
NREM	Nonrapid eye movement
OBS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
$PACO_2$	Alveolar carbon dioxide tension
REM	Rapid eye movement
RV	Residual volume
SDB	Sleep breathing disorder
V'E	Minute ventilation
VC	Vital capacity
Vt	Tidal volume

20.1 Introduction

Breathing is an essential and dynamic process involving complex neural and physiological mechanisms, where there is a constant adaptation to environmental and behavioral conditions in order to maintain blood gas homeostasis throughout life. There is a difference between the breath-

M. Cabral (✉) · B. Mendes · C. Figueiredo
I. Moreira
Hospital de Santa Marta—Centro Hospitalar de Lisboa Central, Lisbon, Portugal
e-mail: mendes.bruno@campus.ul.pt

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_20

ing pattern while awake and asleep. While awake, intentional breathing control takes priority over automatic breathing; in contrast, this changes after falling asleep. Sleep is a period of great vulnerability to ventilation irregularities. The onset of sleep provides some important physiological adjustments in the organism such as reduction in alveolar ventilation and chemosensitivity, as well as an increase in upper airway resistance. The presence of respiratory disorders during sleep is very common even in healthy individuals and can result in serious health problems, a lower quality of life, and it is even associated with higher mortality. However, the mechanism that leads to these irregularities are poorly understood due to the absence of models that mimic the complexity of this system.

20.2 Discussion and Analysis of the Main Topic

20.2.1 Sleep Physiopathology

Neurons of the reticular-activating system are essential to the regulation of wakefulness. Sleep is a process that involves complex neural activation. There are two ascending pathways. The first consists of the dorsal root of the cholinergic laterodorsal and pedunculopontine tegmental nuclei, which will activate neurons that promote EEG activity via glutamatergic thalamocortical projections. The second pathway constituted by the ventral root through the hypothalamus includes the serotonergic, noradrenergic, and dopaminergic neurons that originate the aminergic arousal system. Cortical activation is further influenced by orexinergic and cholinergic neurons originating in the hypothalamus and basal forebrain, respectively. During wakefulness, these pathways allow the transmission of sensory information via thalamic gate to areas of the association cortex [1].

The transition from wake to sleep is controlled by homeostatic and circadian processes and occur through a process of reciprocal inhibition between arousal- and sleep-promoting neurons by way of "flip-flop switch." It can be difficult to determine as there is typically brief periods of drowsiness with transient bursts of wakefulness before sleep consolidation. Sleep is divided into two states: rapid eye movement (REM) sleep and non-REM (NREM) sleep, and this different stages of NREM and REM occur repeatedly over the course of a night, in a rhythmical pattern known as a sleep cycle. NREM sleep occurs preferably early in the night and is associated with sleep homeostasis. In turn, REM sleep occurs later in the night and is linked to circadian rhythm of core body temperature [2].

20.2.2 Pulmonary Function

Sleep has a significant effect on the respiratory muscles and therefore ventilation. The transition from wakefulness to non-REM sleep is associated with changes in breathing pattern. During sleep, the breathing control system becomes relatively unstable, due to mechanisms that affect anatomic structures, muscles strength of the upper airway, and arousal threshold. This leads to, and affects the severity of, sleep apnea [3].

During NREM sleep breathing, a reduction in tidal volume (Vt) occurs with depending levels of NREM sleep, as well as minute ventilation (V'E), compared with wakefulness. Respiratory frequency is either increased slightly or unaffected. In REM sleep, a further reduction of 30% in alveolar ventilation and 13% in Vt is observed. The reduction in Vt is attributed to a reduction in ventilator drive as reflected by the decrease in Vt/inspiratory time ratio, whereas respiratory rate is substantially unchanged. The reduction in Vt produces a comparable reduction in V'E during different sleep phases [4].

The ventilatory response to hypercapnia and hypoxia is reduced, particularly during phasic REM, when motor output is reduced and variable in response to a rising chemoreceptor sensory input. During REM sleep, there is inhibition of muscle tone, in particular the intercostal muscles, when respiratory competence depends on the diaphragm. The reduction in alveolar ventilation is associated with an increase in the alveolar carbon dioxide tension ($paCO_2$), which is accompanied by a decrease in both carbon dioxide production and oxygen consumption. Oxygen

saturation is decreased in sleep compared with wakefulness; this decrease is more pronounced in REM sleep [2].

Other changes characterize sleep period such as the reduced size of the pharyngeal airway lumen compared with wakefulness due to hypotonia of the upper airway muscles that occurs with potential upper airway collapse in the presence of partial obstruction. Sleep is associated with a reduction in both efferent activity to the thoracic muscles and a reduction in hypoglossal motor output to the upper airway muscles. The size of the pharyngeal airway lumen is reduced in sleep compared with wakefulness. The patency of the upper airway is dependent on the upper airway size, negative intrapharyngeal pressures, and compliance.

These components are influenced by hypoxia and hypercapnia, sleep/wake transitions, blood pressure, and sex-specific hormones, and a change in them will be accompanied by a decrease in ventilation. In addition, the activation of the pharyngeal dilator muscles can also be influenced by lung volumes.

Both in healthy individuals and in patients with obstructive sleep apnea (OSA), during wakefulness, there is a relationship between upper airway caliber and changes in upper airway volumes. That is, a reduction in lung volumes will lead to increased pharyngeal resistance. During sleep, reduced lung volume leads to increased inspiratory airflow resistance and increased genioglossus muscle activation. Consequently, the pharynx is more collapsible during sleep at low lung volumes.

An increase in total pulmonary resistance during sleep is observed in individuals who do not snore, due to the increase in the neural drive; however it is not significant. On the contrary, in individuals who snore, the increase is more marked, which culminates in changes in the breathing pattern during sleep [4].

In the waking sate, a fast and extremely variable rise in the drive to breathe is prompt by adding resistive or elastic recoil load to the airway which avoid hypoventilation. However, in sleep, this does not happen, that is, the compensatory mechanical response is not so immediate and hypoventilation preserves until chemoreceptor stimuli increase.

Loop gain is a concept that has been used to describe the modulation of breathing during sleep and to explain how changes in respiratory control system can lead to sleep disorders breathing (SDB). Loop gain occur in a context of a feedback system. It is the result of controller gain, plant gain, and feedback gain. The first one, controller gain, refers to the ventilatory response to a change in carbon dioxide and is influenced by hypercapnic ventilatory response and cerebrovascular reactivity. The second one, plant gain, alludes to the efficiency with which ventilation removes carbon dioxide from the body, and the contributing factors are transfer factor (DLCO), metabolic rate, lung volumes, and cardiac output. The last one, feedback gain, is the interval between a change in carbon dioxide in lungs and its transmission to the chemoreceptor which elicits a response. It depends upon a reduction on cardiac output, prolonged circulation time, increased cardiac chamber size, and circulating blood volume. A loop gain >1.0 describes a respiratory system where the response is greater than the insult and so is prone to instability. A loop gain <1.0 describes a system where an insult will be dampened or smoothed out by a response smaller than the insult itself [5].

In patients with OSA, the measurement of loop gain could be a good parameter to assess the individuals predisposed to apnea due to ventilatory instability rather than closure of the upper airway per se [6].

20.2.3 Sleep Disorder Breathing

Sleep disorder breathing forms a group of respiratory disturbance that occurs during sleep and can cause significant reduction in the quality and span of life.

20.2.4 Obstructive Sleep Apnea Disorder

OSA is a complex disorder characterized by recurrent episodes, often cyclical, of breathing cessation (apnea) or reduced amplitude breath (hypopnea), sufficient to cause significant arterial

hypoxemia and hypercapnia. The factors that contribute to apnea events are a compromised extrathoracic upper airway - obstructive event, a marked reduction or cessation of brain stem respiratory motor output - central event, or the combination of both.

The pathogenesis of OSA consists of an altered respiratory mechanics. A decrease in lung volume leads to obstruction of the small airways, which determines a modification in gas exchange and an abnormal response to hypercapnia and hypoxemia [7].

Obstructive events occur at the level of the pharynx, and there are many factors responsible to its collapsibility such as the upper airway anatomy and neuromuscular control, which contribute to variable degrees in each patient. Simply loss of wakefulness inputs to the control of the upper airway and chest wall muscle motor neurons produces serious, short- and long-term consequences to homeostasis and to health. Regarding lung function in OSA, it has been proved a relationship between lung volumes and OSA severity. More precisely, negative relationships were reported between the severity of OSA and expiratory reserve volume, functional residual capacity, forced expiratory volume in 1 s (FEV1), and forced vital capacity (FVC). This way, the reduction in functional residual capacity (FRC) and respiratory system compliance determines an increased work of breathing translated by a high ventilator drive and increased respiratory muscle recruitment [8].

Many other authors have addressed this topic. Appelberg et al. concluded that patients with OSA display an increased ventilatory response to CO_2, reduced end expiratory volume (ERV), and increased closing volume. ERV predicts nocturnal apnea and desaturation frequency to a similar extent as obesity. Also, lung aeration is reduced in the dorsal region during sleep, and patients with OSA display a lower amount of gas in comparison to healthy subjects. Decrease in lung volumes, promoting airway closure, and loss of muscle tone contributed to the altered lung function during sleep [9]. In addition, a significant correlation between mean apnea duration and residual volume (RV) was demonstrated by Zirlik et al [10]. Another relation observed was that a decrease in FEV_1 (even among normal values) was associated with an increased risk of severe OSA, as referred before, but this was not true for $FEV_1 < 60\%$ of predicted. This degree of FEV_1 reduction was a protective factor along with RV > 180% of predicted. This points to a possible protective role of air trapping in OSA severity [11].

The factors that influence the prevalence of OSA, such as obesity, age, and sex, may change the upper airway anatomy. The shape of the oropharynx and hypopharynx becomes more spherical with increasing body mass index (BMI). In addition, the deposition of fat around the upper airways not only influences the upper airway volume but also affects characteristics of the upper airway, mostly, the collapsibility. Furthermore, in lean OSA patients, the anatomy of the upper airway is correlated with the apnea/hypopnea index (AHI), demonstrating that the anatomy of the upper airway in the obese patients is only one of the many factors that influences the upper airway occlusion.

A sleep-related reduction in the neural drive results in a relatively small increase in total lung resistance in nonobese people who do not snore, but this increase is much more pronounced in patients who snore. That is why the upper airway patency is compromised during sleep which results in changes in ventilatory mechanics during that period that leads to obstructive SDB. In addition, the narrowing of the upper airway during inspiration and exhalation that occurs in healthy individuals during non-REM sleep will once again be exacerbated in people who snore or have SDB. Although there is an important narrowing of the airway lumen in inspiratory time, it is a fact that this narrowing will end up not having such a great impact on the airway closure. Relatively, at the end of expiration, the cross-sectional area of the upper airway lumen is determined by the narrowing during the mid-to-late expiratory time, which will result in the closure of the airway, and therefore in an obstructive apnea. Curiously, a reduction in the lumen and the collapse of the upper airway are also observed in central sleep apnea, when intrathoracic pressure does not become more negative. This way,

the collapse of the upper airway will prompt the reflex inhibition of phrenic nerve activity which in turn will prolong the apnea [4].

20.2.5 Central Sleep Apnea Syndrome

Central sleep apnea (CSA) is defined by recurrent cessations of airflow and simultaneous reduction of the breathing effort. In contrast to OSA, ventilatory impulses generated by the brain stem are lacking in CSA.

Cheyne-Stokes breathing pattern is a subgroup of CSA. It is characterized by a specific form of periodic breathing (waxing and waning amplitude of flow or Vt) with a crescendo-decrescendo pattern of respiration between apneas and hypopneas.

There are also other subgroups of CSA syndrome such as central sleep apnea due to high altitude periodic breathing, medical condition or drug, and primary sleep apnea of infancy.

20.2.6 Sleep-Related Hypoventilation Syndromes

Hypoventilation syndrome is characterized by a $paCO_2 > 55$ mmHg for >10 min or an increase of >10 mmHg in $paCO_2$ during sleep comparatively to wakefulness, according to the 2012 American Academy of Sleep Medicine Guidelines. Nocturnal hypoventilation is associated with a decrease in the ventilatory drive, respiratory iatrogenic depression, alteration of respiratory nerve conductance, muscular disease, chest wall deformities, and severe obesity. This happens because, during sleep, the response to hypercapnia and hypoxemia is greatly reduced in REM and not so much in NREM, which leads to dysrhythmic breathing. Also, REM sleep alters upper airways patency. Consequently, there are changes in ventilation due to changes in volume/minute, Vt, and dead space.

When breathing problems are corrected at an early stage of the disease, mainly with nocturnal noninvasive ventilation, quality of life and life expectancy improves. An intervention later on is rarely successful [2].

20.2.6.1 Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) is the most common sleep-related hypoventilation syndrome. It is characterized by hypercapnia ($paCO_2 > 45$ mmHg) during wakefulness in obese patients (BMI > 30 kg/m^2). Some patients, contrarily to OSA, can have AHI < 5 events/hour although in most cases obstructive apneas are seen. These patients frequently present with mild restrictive pattern due to increased thoracic impedance.

The pathogenesis of OHS is characterized by a respiratory mechanism disturbance, based on a decrease of FRC as well as a reduced respiratory system compliance. Therefore, an increase in work of breathing is observed, which determines a high ventilator drive and an increase in recruitment of respiratory muscles. In addition, the decrease in lung volumes below the closing capacity is responsible for the obstruction of the small airways that will determine an impairment of gas exchange and changes in the ventilatory response to hypoxemia and hypercapnia. The latter are, in part, associated with chronic hypoxemia and poor sleep quality. Overall, all of this will end up with worsened nocturnal hypercapnia and nocturnal hypoxemia.

Furthermore, obesity when associated with OSAS increases the severity of pulmonary function and alveolar-capillary diffusion alteration. This can be explained in part by the alveolar inflammation being that the role of adipocytokines in systemic inflammation has been proved by many studies [12].

Alteration of ventilatory control and sensitization of chemoreceptors are also due to hypothalamic dysfunction and hormonal influences. In obesity and OHS, leptin levels are increased; however, the function of this hormone is also altered implying a state of resistance to leptin.

OHS is a significant cause of chronic respiratory failure and, in this sequence, an important indication for noninvasive ventilation (NIV), both in acute and in chronic situations. The intro-

duction of the NIV will allow the resting of the respiratory muscles, an increase in thoracic compliance, and resetting of the respiratory centers. The results of this therapy will be translated by a rapid and sustained improvement of daytime arterial blood gas levels and a net reduction of daytime sleepiness. In the long run, it is known that hospitalizations for respiratory and heart illness decrease in the 3 years after the initiation of NIV. Overall, NIV is cost-effective and improves morbidity and mortality in OHS patients [1].

20.2.6.2 Neuromuscular Disorders

Sleep-related hypoventilation syndrome can also be associated with a medical condition such as neuromuscular disease (NMD). NMD is divided into subgroups depending on the site and the etiology of involvement. They can be caused by impairment of the motor unit comprising the motor neuron, nerve root, myoneural junction, and muscle, as exemplified in Table 20.1.

Hypoventilation is the hallmark of SDB in NMD. The involvement of respiratory muscles makes NMD patients vulnerable to SDB with a significant prevalence of SDB among such patients. The gradual deterioration of muscle strength is what best characterizes NMD. All muscles can be affected but the most important ones are the respiratory muscles, because their involvement can result in respiratory failure. Thus, the prognosis in NMD depends mainly on respiratory muscle strength.

Respiratory muscle weakness, increased respiratory load on an already weak diaphragm, and the inadequacy of central drive to breathe are the basis of SDB. Patients with NMD have more shallow breathing due to less capacity for lung expansion, which results in small bronchiectasis and decreased lung compliance. Other factors that contribute to less lung expansion are muscle atrophy, extra-articular contractures, and intra-articular adhesions. Also spinal deformities, such as scoliosis, can affect the contractility of respiratory muscles. All of these mechanisms end up forming a vicious cycle.

The involvement of respiratory system is the most serious complication and the leading cause of mortality, as enhanced before. In progressive NMD, with progressive diaphragm involvement, respiratory insufficiency occurs initially in REM sleep, followed by REM and NREM, and in last stage of the disease in sleep and wakefulness, once vital capacity (VC) falls below 40%.

A decrease in airflow and alveolar ventilation leads to a decrease in vital capacity and gas exchange in addition to a mismatch of ventilation/perfusion. This decrease in VC associated with a progressive increase in diaphragm involvement increases the susceptibility to SDB. VC decreases at an earlier stage of the disease compared to total lung capacity, which also leads to an increased in RV, and for this reason, these patients present with a restrictive pattern. The nocturnal hypoventilation in these pathologies causes gradual diurnal hypoventilation.

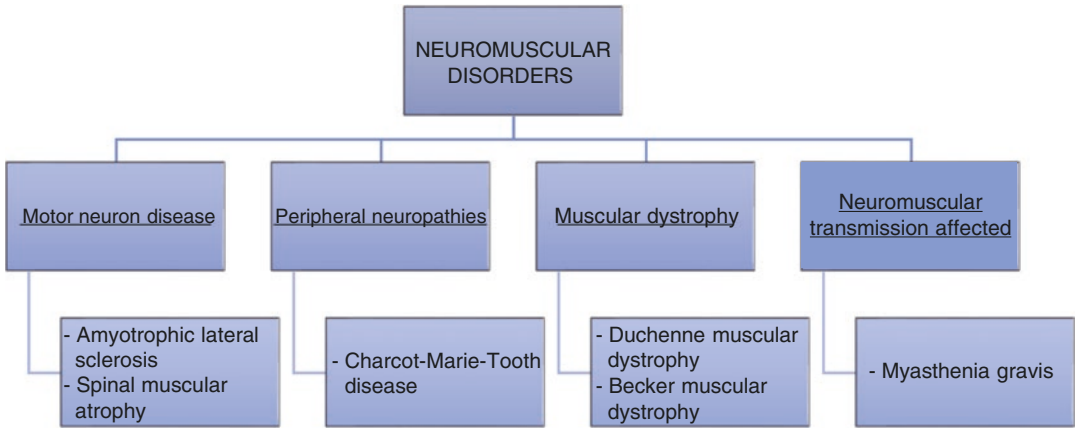

Table 20.1 Neuromuscular disorders

The type of sleep disorder will depend on the type and stage of NDM, more precisely, which muscles are involved. When the upper airway or intercostal muscles are mainly involved, obstructive events will predominate. If, on the other hand, it is the diaphragm that is most affected, then what will dominate is nocturnal hypoventilation. So in addition to hypoventilation, also central and obstructive events will occur. As an example, in brainstem lesions like in Arnold-Chiari malformation, the most affected muscles are the abdominals and those of the upper airway. Such patients are particularly vulnerable to central apnea. Furthermore, NMD predisposes to OSA because of bulbar dysfunction, pharyngeal muscle weakness, and macroglossia (such as in muscular dystrophies). In patients with preserved diaphragmatic function, as is the case with type 2 spinal muscular atrophy, during sleep, there is a slight hypoxemia and a slight increase or even a normal $paCO_2$ [13].

20.2.6.3 Congenital Central Hypoventilation Syndrome

In cases of congenital central hypoventilation syndrome, the ventilatory response to imposed hypercapnia and to hypoxemia is absent. Initially, hypoventilation is most marked during NREM sleep. In more advanced stages of the disease, hypoventilation begins to appear in other stages of sleep and even when the patient is awake. The prognosis is reserved since the child will need mechanical NIV in less severe situations and tracheostomy in more severe cases, as much as lifetime mechanical assistance. In recent years, due to advances in this area, early diagnosis and guidance has improved outcomes [6].

20.2.6.4 Others

Sleep-related hypoventilation may also have other etiologies due to medication or medical disorders, such as interstitial lung diseases or sick cell hemoglobinopathies.

When all the previous etiologies have been ruled out, it is considered idiopathic sleep-related nonobstructive alveolar hypoventilation, a rare disorder.

In addition, patients with COPD, bronchiectasis, and cystic fibrosis also have an obstructive disorder. The hypoxemia and hypercapnia registered during the wakefulness worsens at sleep, especially in REM. In COPD, nocturnal hypoventilation can be found, particularly in those with FEV1 < 1000 ml. This is due to increased work of breathing, overloaded respiratory mechanics, and malnutrition [14].

20.3 Conclusion Discussion

Sleep is essential, but poses a risk to breathing in some individuals. The term SDB encompasses a spectrum of abnormalities from simple snoring to complete closure of the upper airway. There are important differences in lung functions between patients with SDB and normal subjects. A better understanding of the pathophysiologic mechanisms of SDB and consequently lung function will lead to an improved clinical management of the disease, from early diagnosis to more targeted therapies.

Key Major Recommendations

- The transition from wakefulness to sleep is associated with changes in breathing pattern, and sleep is a period of great vulnerability to ventilation irregularities.
- Sleep disorder breathing form a group of respiratory disturbance that occurs during sleep and can cause significant reduction in the quality and span of life.
- The term sleep disorders breathing encompasses a spectrum of abnormalities from simple snoring to complete closure of the upper airway.
- In these diseases, lung function can provide tools to establish the diagnosis and guide the therapy with noninvasive mechanical ventilation.

References

1. Backer W, Bloch K, Brack T, et al. Sleep and control of breathing disorders. In Palange P, Rohde R. European Respiratory Society Handbook of Respiratory Medicine. United Kingdom, UK, 2019;522–540.
2. Primhak R, Kingshott R. Sleep physiology and sleep-disordered breathing: the essentials. BMJ 2012;97:54–58.
3. Choi E, Park DH, Yu JH, et al. The Severity of Sleep Disordered Breathing Induces Different Decrease in the Oxygen Saturation During Rapid Eye Movement and Non-Rapid Eye Movement Sleep. Psychiatry Investig. 2016 Nov; 13(6):652–658.
4. McKay LC, Attalla A, Morrell MJ. Physiology and neural control of breathing during sleep. In: McNicholas WT and Bonsignore MR, et al. European Respiratory Society, Respiratory Monograph. United Kingdom, UK, 2010;50:1–16.
5. Diaz ND, Malhotra A. Inherent vs. Induced Loop Gain Abnormalities in Obstructive Sleep Apnea. Front Neurol. 2018;9:896.
6. Dempsey J, Veasey SC, Morgan BJ, et al. Pathophysiology of Sleep Apnea. Physiol Rev 2010;90:47–112.
7. Verbraecken J., Andreas S, Randerath W, et al. Respiratory conditions. In: Simonds AK, Backer W, ed. European Respiratory Society, Handbook of Respiratory Sleep Medicine. United Kingdom, 2021; 21–51.
8. Bikov A, Losonczy G, Kunos L. Role of lung volume and airway inflammation in obstructive sleep apnea. Respiratory investigation 2017.
9. Appelberg J. Ventilation and Lung Volume During Sleep and in Obstructive Sleep Apnea. Acta Universitatis Upsaliensis. Comprehensive Summaries of Uppsala Dissertations from the faculty of Medicine 1246.
10. Zirlik S, Schahin SM, Premm W, Hahn EG,et al. Lung volumes and mean apnea duration in obstructive sleep apnea. Respiratory Physiology & Neurobiology 2009; Volume 168, Issue 3, Pages 303–305.
11. Santos MA, Aguiar M, Sacramento V, et al. Obstructive Sleep Apnea severity and lung function. European Respiratory Journal 2018 52: PA2522.
12. Rouatbi S, Ghannouchi I, Kammoun R, et al. The Ventilatory and Diffusion Dysfunctions in Obese Patients with and without Obstructive Sleep Apnea-Hypopnea Syndrome. J Obes 2020.
13. Albdewi MA, Liistro G, El Tahry R. Sleep-disordered breathing in patients with neuromuscular disease. Sleep Breath 2017.
14. American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.

Chronic Heart Failure

21

Ahmet Cemal Pazarlı

Abstract

Chronic heart failure (CHF) is currently an important health problem causing significant mortality and morbidity. There are highly effective medical treatments used in the treatment of chronic heart failure, and standard treatment guidelines provide the most efficient treatment benefits. Noninvasive ventilation (NIV) treatment modalities used in chronic heart failure have provided significant benefits in the clinical outcomes of the disease in recent years. The selection of these treatment modalities by the relevant clinicians and learning the clinical applications would make a great contribution to the treatment of patients with cardiovascular diseases.

Keywords

Chronic heart failure · Noninvasive ventilation · Sleep-disordered breathing · Continuous positive airways pressure · Adaptive servo-ventilation

Abbreviations

AASM	Academy of Sleep Medicine
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AHI	Apnea-hypopnea index
ASV	Adaptive servo-ventilation
Bi-PAP	Bi-level positive airway pressure
CHF	Chronic heart failure
CPAP	Continuous positive airways pressure
CSA	Central sleep apnea
CSB	Cheyne-Stokes breathing
ESC	European Society of Cardiology
HF	Heart failure
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
SDB	Sleep-disordered breathing
ST	Spontaneous time

21.1 Introduction

Heart failure (HF) is a clinical syndrome caused by structural or functional cardiac abnormalities, and it is characterized by typical symptoms such as shortness of breath, ankle edema, and fatigue as a result of low cardiac output and increased intracardiac pressures during rest or exercise by

A. C. Pazarlı (✉)
Department of Chest Diseases, Gaziosmanpaşa University Faculty of Medicine, Tokat, Turkey

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_21

signs of increased jugular venous pressure, pulmonary rales, and peripheral edema [1]. In other words, it is the inability of the heart to pump sufficient blood that can meet the metabolic needs of the body without the lack of filling. Patients with HF are often described as "chronic HF" for a while. The term "stable" is used for patients whose symptoms and signs have been under control for at least 1 month with treatment. If the chronic stable HF deteriorates, the patient can be described as "decompensated," and this situation may develop as "acute," requiring admission to the hospital.

For example, as a result of acute myocardial infarction, a person with acute asymptomatic cardiac dysfunction for an unknown time may appear in a subacute (gradual) clinical manifestation, and the cardiac symptoms may continue or the patient may become "compensated" by healing. Although the clinical symptoms and signs of the patients are relieved, the underlying cardiac dysfunction may not improve, and in this case, patients are at risk for recurrent "decompensation." The term "congestive HF" is still used from time to time, especially in the USA, and describes acute or chronic heart failure (CHF), which is evidence of congestion (water and salt retention). These terms can be used at different times for the same patient depending on the stage of the disease [1].

It is of great importance to identify and treat the main etiology that causes HF and to control the factors that can precipitate HF to provide the most effective treatment strategy for CF. Although rapid relief is provided in most patients with diuretics, vasodilators, inotropic agents, and supplemental oxygen therapy in standard HF treatment, some patients have no or only a partial response to treatment. Especially hypoxemic (Type 1) respiratory failure may develop, and some patients may require mechanical ventilation due to accompanying hypercapnia and respiratory acidosis.

In this section, it is aimed to discuss noninvasive treatment strategies in CHF in the light of the current literature and guidelines rather than medical and surgical treatments of CHF.

21.2 Discussion and Analysis of the Main Topic

HF is a chronic condition that tends to get worse over time. The disease continues for life in most cases. Only a small group of patients with HF experience temporary improvements in their clinical course. Depending on the reason, the progression of HF varies from person to person. In CHF, cardiac performance can worsen gradually over the course of months or years and the heart chambers then dilate gradually. Clinical worsening may develop, and patients need to be hospitalized from time to time.

Oral medication for the treatment of HF should be used for a lifetime to prevent or slow down the progression of the course of HF over time, worsening of the clinical features, dilatation of the heart chambers, and decrease in cardiovascular performance, and it prevents deaths due to HF.

The use of interventional therapies for the treatment of CF is very important as well as many oral treatment options that are accepted to be effective. Considering the developments in recent years and understanding of the pathophysiology of the disease, noninvasive ventilator (NIV) therapies have taken their place in the guidelines in the treatment of HF and are used successfully. NIV therapies for the diagnosis and treatment of acute and chronic heart failure are recommended by the 2016 European Society of Cardiology (ESC) guidelines [1]. According to this guideline, it has been reported that noninvasive ventilation therapy with end-expiratory positive airway pressure (PAP) improves left ventricular function by reducing left ventricular afterload and reduces the need for intubation and short-term mortality in acute cardiogenic pulmonary edema. Furthermore, it is recommended to be used as quickly as possible in acute cardiogenic pulmonary edema and hypertensive acute heart failure, and with caution in cardiogenic shock and right ventricular failure [1]. Besides, the initiation of NIV might acutely improve cardiac function. Cardiac hemodynamics of long-term NIV depends on the underlying conditions that lead to heart failure.

The main symptoms in CHF are exercise, which limits exercise tolerance, dyspnea during daily living activities, fatigue, and dyspnea that develops at rest in the later periods. Exercise dyspnea or exercise intolerance is associated with abnormal respiratory function. The mechanism of HF involves chronotropic incompetence, reduced myocardial β-adrenoceptor density and sensitivity, impaired diastolic function consecutive to myocardial and vascular remodeling with reduced cardiac output, impaired tissue oxygen utilization, abnormal skeletal muscle metabolism, dysregulation of skeletal muscle blood flow, and hyperventilation caused by elevated physiologic dead-space in the edematous lung [2].

An important issue in CHF is the high prevalence of central sleep apnea and sleep-disordered breathing (SDB) such as Cheyne-Stokes breathing (CSB) and obstructive sleep apnea (OSA). SDB affects the prognosis of patients with CHF and causes their functional capacity to deteriorate, reducing their quality of life and increasing mortality rates. It has been reported that approximately 69–76% of patients with CHF have SDB [3]. The evidence so far has shown that SBD accelerates disease progression in patients with CHF. SBD increases blood pressure and left ventricular afterload by inducing hypoxia and hypercapnia, causing the autonomic tone imbalance by sympathetic activation and parasympathetic inhibition which are all important stimuli for myocardial ischemia, reverse cardiac remodeling, and left ventricular dysfunction [4].

NIV is increasingly being used to treat patients with chronic hypercapnic respiratory failure of different etiologies [5]. Although NIV is commonly used in the treatment of acute heart failure in cardiorespiratory disorders, several modes of NIV have now been investigated to treat CHF.

NIV modalities that have been proven with their effectiveness for CHF are continuous positive airways pressure (CPAP), bi-level positive airway pressure (Bi-PAP), and adaptive servo-ventilation (ASV).

21.2.1 Continuous Positive Airways Pressure (CPAP)

CPAP treatment in CHF is the most commonly used and researched NIV modality. CPAP through a nasal mask contributes positively to the treatment of HF by preventing pleural pressure fluctuations during breathing and reducing heart rate variability. CPAP application is associated with myocardial transmural pressure, left ventricular afterload, and sympathetic activity decrease, and CPAP treatment increases left ventricular ejection fraction by 25–34%. Furthermore, CPAP improves myocardial blood demand and supply (oxygenation), and it can relieve arrhythmias and prevent long-term cardiovascular events [6]. One of the leading causes contributing to the development and/or progression of heart failure is sleep-disordered breathing in these patients. Cheyne-Stokes breathing (CSB) and central sleep apnea (CSA) can be seen in patients with heart failure and make the treatment more difficult causing arrhythmia and sudden death. Obstructive sleep apnea is found in 5–30% of HF patients; central sleep apnea syndrome is detected in 30–60% [3]. It has been suggested that venous congestion that develops in the upper airway in HF may narrow the upper airway and thus increase airway resistance and cause obstructive sleep apnea syndrome. Pulmonary congestion, which is developed by heart failure, causes tachypnea and hyperventilation by stimulating the pulmonary vagal receptors resulting a decrease in apnea threshold due to hypercapnia, and then central apnea occurs.

The most important study conducted so far in patients with HF and SDB is CANPAP study. In the study of Bradley et al. [7], 258 CHF patients with CSA were randomized as with or without CPAP in treatment and followed for 2 years. In the first 3 months, statistically significant improvement was observed in the mean apnea-hypopnea index (AHI), nocturnal oxygen desaturation, and 6-min walking test results in the group using CPAP compared to the control group, while there was no difference in terms of quality of life,

time without transplantation or hospitalization. Arzt et al. [8] conducted the post hoc analysis of the study and found a statistically significant difference in the patient group with CSA using CPAP, whose AHI was reduced to <15, compared to the control group in terms of the time spent without transplantation. A meta-analysis including six randomized studies showed that CPAP was associated with a 5% improvement in ejection fraction in HF and OSA patients [9]. In a randomized study that directly compared CPAP with Bi-PAP, it was shown that there was more improvement in cardiac function compared to patients who received BI-PAP [10]. These shreds of evidence suggest that CPAP can improve outcomes in HF in patients with persistent SDB despite CHF optimization. The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) 2013 guidelines for the management of patients with HF support use of CPAP therapy in patients with HF and SDB to increase left ventricular ejection fraction and improve functional status [11].

As can be seen from the results of recent clinical studies, CPAP continues to be the first standard treatment option in cases where positive airway pressure therapy use is considered in patients with CHF and sleep-disordered breathing. There are still ongoing studies on comparative research with other PAP modalities and aiming to explore the advantages and disadvantages of CPAP such as effectiveness and compliance.

21.2.2 Adaptive Servo-Ventilation (ASV)

ASV is an NIV device designed to meet the ventilation support of patients by providing inspiratory positive airway pressure (IPAP) and to adjust the rate of change of airflow by detecting the patient's inspiratory changes.

In a meta-analysis of 14 randomized trials (n = 538) comparing ASV with control groups (subtherapeutic ASV, CPAP, supplemental oxygen, or no treatment) in patients with stable HF, it has been reported that ASV has been shown to significantly improve left ventricular ejection fraction and exercise capacity predominantly in patients with CHF and SDB [12].

The treatment of predominant CSA by ASV in patients with HF (SERVE-HF) trial, which can be considered as the milestone study in its field, investigated the effects on cardiovascular outcomes and survival to adding ASV to medical treatment in patients who have low EF (EF <45%) with accompanying SDB (with CSA). All-cause and cardiovascular mortality were found to be higher in the ASV group than in the control group. Adding ASV to medical treatment did not improve clinical outcomes in patients with HF with low EF and accompanying CSA. Although ASV reduced CSA, it was observed that it increased the risk of cardiovascular death by 34% and did not affect HF symptoms and quality of life. However, researchers recommended that these results could not be generalized to patients with preserved EF and those with predominantly obstructive sleep apnea. Moreover, it was suggested that patients with EF < 45% and predominantly CSA should not apply ASV until the opposite was shown [13].

Decisions whether to continue or discontinue treatment in patients currently being treated with ASV should be personalized after reassessing the balance of risks and benefits. Recommendations for the use of ASV in CHF patients have been updated in the American Academy of Sleep Medicine (AASM) and ESC guidelines recently [1, 14]. The ongoing ADVENT-HF study could help to understand the role of ASV in this patient population [15].

21.2.3 Bi-Level Positive Airway Pressure (bi-PAP)

The different hemodynamic effects of Bi-PAP compared to CPAP may be due to a lower increase in end-expiratory lung volume secondary to low expiratory positive airway pressure (EPAP). The effects of BIPAP in patients with HF were shown mostly by studies conducted on patients who cannot tolerate CPAP. It has been reported that BIPAP therapy in patients with CHF and SDB has a beneficial effect on both

abnormal breathing patterns and impaired heart function [16]. In addition, it has been noted that BIPAP can be an effective alternative for HF and pure CSA/CSS patients who do not respond to CPAP [17]. In a meta-analysis, it was stated that BI-PAP treatment in spontaneous time (ST) mode can be considered optionally, only for the treatment of SDB patients with CHF who have no response to adequate trials of CPAP, ASV, and oxygen therapies [18].

21.3 Conclusion Discussion

CHF is a serious medical condition. When a patient is acutely diagnosed, the earlier CHF is diagnosed and treatment started, the better the chance of successful treatment and the patient's chances of survival. It is important that SDBs, which are seen at a high rate in CHF patients, should be examined carefully, and the decision of NIV use and the type of NIV should be decided correctly. Although CPAP is an essential NIV option that is linked to clinical effectiveness in patients with HF, ASV and BIPAP treatment modalities should also be kept in mind for certain patient groups.

Key Recommendations

- Performance status for patients with a diagnosis of CHF should be properly evaluated, and it should be ensured that they receive an adequate standard of medical treatment.
- SDB, which is frequently observed in patients with CHF, should be diagnosed correctly, and NIV modality selection should be made and applied according to patient characteristics. This will make a significant impact on the prognosis of the disease.
- CPAP should be the first-line treatment choice among NIV treatment modalities in patients with CHF and SDB. However, other modalities such as ASV and BIPAP should be considered in patients who cannot tolerate CPAP according to their clinical characteristics.
- It should be noted that NIV therapies require ideal conditions and regular follow-up. Treatment should be started as soon as possible after the diagnosis.

References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J. 2016;20
2. Bündchen DC, Gonzáles AI, Noronha MD, et al. Noninvasive ventilation and exercise tolerance in heart failure: a systematic review and meta-analysis. Braz J Phys Ther. 2014;18(5):385–94.
3. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol. 2007;49:1625–31.
4. Bradley TD, Floras JS. Sleep apnea and heart failure: part II: central sleep apnea. Circulation. 2003;107(13):1822–6.
5. Janssens JP, Derivaz S, Breitenstein E, De Muralt B, Fitting JW, Chevrolet JC, Rochat T. Changing patterns in longterm noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. Chest. 2003;123:67–79.
6. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. Chest. 2005;127:2076–84.
7. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353:2025.
8. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian continuous positive airway pressure for patients with central sleep apnea and heart failure trial (CANPAP). Circulation. 2007;115:3173.
9. Sun H, Shi J, Li M, Chen X. Impact of continuous positive airway pressure treatment on left ventricular ejection fraction in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. PLoS One. 2013;8:e62298.
10. Khayat RN, Abraham WT, Patt B, et al. Cardiac effects of continuous and bilevel positive airway pressure for patients with heart failure and obstructive sleep apnea: a pilot study. Chest. 2008;134:1162.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2013;62:e147.
12. Sharma BK, Bakker JP, McSharry DG, et al. Adaptive servoventilation for treatment of sleepdisordered breathing in heart failure: a systematic review and meta-analysis. Chest. 2012;142:1211.
13. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373(12):1095–105.

14. Aurora RN, Bista SR, Casey KR, et al. Updated adaptive servo-ventilation recommendations for the 2012 AASM guideline: "the treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses". J Clin Sleep Med. 2016;12:757.
15. https://clinicaltrials.gov/ct2/show/study/NCT01128816.
16. Kasai T, Narui K, Dohi T, et al. Efficacy of nasal bi-level positive airway pressure in congestive heart failure patients with cheyne-stokes respiration and central sleep apnea. Circ J. 2005;69:913.
17. Dohi T, Kasai T, Narui K, et al. Bi-level positive airway pressure ventilation for treating heart failure with central sleep apnea that is unresponsive to continuous positive airway pressure. Circ J. 2008;72:1100.
18. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35:17.

Respiratory Physiotherapy and Pulmonary Rehabilitation

22

Bruno Cabrita, Gil Gonçalves, André Cabrita, and Énio Pestana

Abstract

Pulmonary rehabilitation is considered one of the most important treatment strategies of chronic pulmonary patients. It consists in an evidenced-based multidisciplinary and individually tailored approach to the patient that includes exercise training, education and behavior change with the purpose of managing symptoms and the disease, promoting a healthy lifestyle, autonomy, social skills, and long-term adherence to health-enhancing behaviors.

Keywords

Rehabilitation · Physiotherapy · Lung · COPD · Treatment

Abbreviations

6MWT	Six-minute walk test
CAT	COPD Assessment Test
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Questionnaire
ILDs	Interstitial lung diseases
IMT	Inspiratory muscle training
ISWT	Incremental shuttle walk test
mMRC	Modified British Medical Research Council
NIV	Noninvasive ventilation
NMES	Neuromuscular electrical stimulation
PR	Pulmonary rehabilitation
RPE	Ratings of perceived exertion
SGRQ	St. George's Respiratory Questionnaire

22.1 Introduction

22.1.1 What Is Pulmonary Rehabilitation?

Pulmonary rehabilitation (PR) is considered one of the most important and cost-effective treatment strategies in the management of chronic pulmonary patients (Fig. 22.1). It consists in an evidenced-based multidisciplinary and individually tailored approach to the patient that

B. Cabrita (✉)
Pulmonology Department, Hospital Pedro Hispano, Matosinhos, Portugal

G. Gonçalves
Pulmonology Department, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

A. Cabrita
Cardiology Department, Centro Hospitalar Universitário São João, Porto, Portugal

É. Pestana
Rehabilitation Department, Hospital CUF Cascais, Lisbon, Portugal

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_22

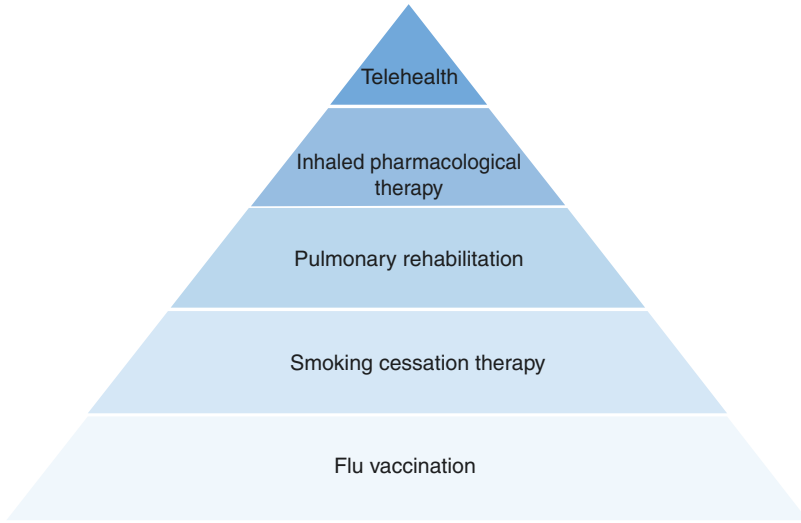

Fig. 22.1 Cost-effectiveness of chronic pulmonary diseases treatment strategies[2]

includes exercise training program, education and behavior change with the purpose of managing symptoms and the disease, promoting a healthy lifestyle, autonomy, social skills, and also a long-term adherence to health-enhancing behaviors [1–5]. The multidisciplinary team involved in the program may be constituted by physicians, physiotherapists, psychologists, and dieticians [1, 3].

22.1.2 Why Is Pulmonary Rehabilitation Important?

Chronic respiratory diseases have significant morbidity and mortality worldwide, with a prevalence of more than 10% of the population. They include chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma, and interstitial lung diseases (ILDs). These conditions manifest with symptoms like exertional dyspnea and cough, which lead to exercise avoidance with progressive loss of muscle mass and function. PR aims at interrupting this vicious cycle of physical and social deconditioning, helping patients control their symptoms and their disease, tolerance to physical daily activities, and reducing healthcare need and costs. It also lowers the incidence of anxiety and depression and increases quality of life [1–4]. PR is considered one of the most cost-effective treatments of chronic pulmonary diseases currently available [1, 3].

22.1.3 Is Pulmonary Rehabilitation Widely Available?

PR remains significantly underutilized worldwide, mainly due to the lack of referral, institutional resources and inaccessibility from patients [4]. Data from an ERS COPD audit performed in 13 countries reported that only 30% of eligible COPD patients receive PR, 35% hospitals implement hospital PR, 16% implement home-based PR, and 30% implement both strategies [3].

22.2 Discussion and Analysis of the Main Topic

22.2.1 Which Patients Should Enroll in a Pulmonary Rehabilitation Program?

PR should be offered to patients with chronic pulmonary diseases, including COPD, bronchiectasis, cystic fibrosis (CF), asthma, and ILDs that remain symptomatic or have functional limitations despite adequate medical therapy [1–4, 6]. PR should also be offered to patients with

Table 22.1 List of other conditions than COPD, for which PR may be beneficial [8]

Non-COPD respiratory disorders for which PR may be beneficial
Other conditions associated with airflow obstruction:
Asthma
Cystic fibrosis (CF)
Non-CF diffuse bronchiectasis
Respiratory disorders associated with restrictive physiology:
ILD/pulmonary fibrosis
Acute respiratory distress syndrome survivors
Restrictive chest wall disease (scoliosis or kyphosis)
Selected patients with neuromuscular disease
Obesity-related respiratory disorders
Other respiratory conditions:
Pulmonary hypertension
Lung cancer
Before and after lung transplantation
Respiratory impairment related to spinal cord injury

lung cancer, lung surgery, or transplantation and patients with pulmonary hypertension [4].

Disorders other than COPD for which PR can be beneficial are shown in Table 22.1 [7].

22.2.2 Which Patients Should Not be Referred to a Pulmonary Rehabilitation Program?

Exclusion criteria include unstable cardiac diseases, severe motor or neurologic diseases, severe cognitive or psychiatric impairment, and terminally ill patients [1, 2].

22.2.3 What Are the Benefits of Pulmonary Rehabilitation?

Benefits of PR are described in the literature and resumed in Table 22.2. They include:

- *Exercise capacity:* Cochrane Reviews have shown significant benefits of a PR program in chronic respiratory diseases. Patients improve their exercise capacity, showing an increase of 48 m in 6-min walk test (6MWT) and 75.9 m in incremental shuttle walk test (ISWT) [1–3].

Table 22.2 Benefits of pulmonary rehabilitation in patients with chronic pulmonary diseases

Benefits of pulmonary rehabilitation
Improved quality of life
Improved exercise capacity
Improved functional capacity
Improved muscle strength
Improved anxiety and depression levels
Improved self-efficacy and autonomy
Improved knowledge
Improved disease control
Improved symptoms control
Reduced hospitalization
Reduced health care costs
Improved survival

- *Physical activity levels:* Studies show that PR contribute to a small but significant increase in physical activity, improving survival and quality of life and decreasing healthcare utilization. However, since studies lack a control group, these data may be difficult to interpret [1, 2].
- *Muscle strength:* Muscle weakness is an important systemic marker of chronic pulmonary diseases, in particular COPD patients, since it is associated with worse prognosis, higher morbidity, and mortality. PR programs have demonstrated improvement in muscle strength, compared with usual care [1, 2].
- *Symptoms and quality of life:* Cochrane Reviews also evidence an increase in health status [evaluated by the St. George's Respiratory Questionnaire (SGRQ)], dyspnea, and fatigue levels [evaluated by Chronic Respiratory Questionnaire (CRQ) and COPD Assessment Test (CAT)] [1, 2].
- *Daily living activities:* Although not yet reported in a randomized clinical trial, PR has shown significant improvements in self-reported measures of daily living activities in some studies [1, 2].
- PR also improves patients' self-efficacy scores. Self-efficacy measures the levels of confidence to successfully complete a chosen task and is an important outcome, since it is associated with adherence to PR [1, 2].
- *Disease control:* PR has proved benefits in the control of chronic pulmonary diseases, pre-

vention of exacerbations, and complications, therefore, contributing to reduce healthcare need and costs, as well as morbidity and mortality [3].

- *Psychological status:* PR has demonstrated a significant improvement in patients' depression and anxiety levels [1, 2].
- *Nutritional status:* Studies of the effect of PR in nutritional status have shown variable results and a minor effect on body weight. Also, retrospective data showed that baseline nutritional status has no influence in the outcomes of a PR program [1, 2].
- *Survival:* One randomized clinical trial with stable COPD patients found no statistical difference on survival when comparing patients who received PR with a control group; however, the study may have been underpowered to detect a mortality difference between the groups [1, 2]. Physical activity levels are the strongest predictor of all-cause mortality in COPD patients, and PR is a strategy that promotes a healthy lifestyle, exercise tolerance, and adherence, contributes to a better disease control, reduces morbidity, exacerbations, and hospital admissions, and, consequently, increases survival [3].

It is currently unknown the real impact of PR in mortality, due to a lack of studies. The benefits of PR are so well established that it is considered unethical to include a control group without offering PR; therefore, the real benefits in mortality will probably remain unquantified [3].

22.2.4 Referral Process and Initial Assessment

Patients should be informed about the benefits of enrolling in a PR program, and their concerns should be addressed, since it has been demonstrated that this may influence PR benefits and completion. The aims of enrolling the program should be discussed and patients should know that, although dyspnea and fatigue limit their daily activities, they may improve their exercise capacity and quality of life with PR [1, 2].

The initial evaluation is completed by the PR staff and includes a full patient history, physical examination, and assessment of contraindications and risk factors, such as unstable cardiovascular disease (unstable angina, unstable arrhythmias, aortic aneurysm, hypertension), or other inhibiting conditions, such as severe arthritis or neurological conditions [8]. An exercise assessment is recommended to individualize the exercise prescription and evaluates the potential need for supplemental oxygen [1, 9]. This may include a maximal cardiopulmonary exercise test (including ventilation and gas exchange assessment and a standardized ramp protocol) to evaluate the safety of exercise, define the factors contributing to exercise limitation, and identify a suitable exercise prescription. Submaximal exercise testing may be used depending on the rationale for the test and the patient's clinical status [1, 9]. Referral to a specialist when necessary should be determined prior to commencing [8].

Patients should be informed about the PR program, including the description of the group sessions of physical exercise. Additionally, using cognitive behavioral techniques before enrolling patients in a PR program has demonstrated benefits, with improved adherence rates [1, 2].

Finally, the key requirement for staff delivering the program is clinical competence, which requires skills and knowledge to ensure patient safety [1].

There are particularities and conditions concerning patients and their participation in PR that need to be considered:

- *Smokers:* Although studies evidence that smokers tend to have lower adherence to a PR program, it is known they have the same benefit as nonsmokers. Also, this represents an opportunity to facilitate smoking cessation. For this reason, smoking does not represent a contraindication to enroll in PR [1, 2].
- *Chronic respiratory failure:* Patients with chronic respiratory failure (either hypoxemic $PaO_2 < 60$ mmHg or hypercapnic $PaCO_2 > 45$ mmHg) have the same benefit from PR as patients without chronic respira-

tory failure. This should not be a contraindication to training [1, 2].

- *Cardiovascular diseases:* Patients with unstable cardiovascular diseases (unstable angina or arrythmias) should not be referred to PR until stabilization [1, 2]. Studies report that patients with higher cardiovascular comorbidities may have less benefit in quality of life, but similar improvements in dyspnea, compared with other patients. Walking distance has controversial results. PR may also improve cardiovascular risk factors such as high blood pressure [1, 2]. Abdominal aortic aneurysm has higher prevalence in COPD patients. If the aneurysm has <5.5 cm with controlled blood pressure, a PR program including moderate intensity aerobic exercises is considered safe. If the aneurysm has >5.5 cm, mild to moderate aerobic exercise should be safe; however, weight lifting, push-ups or sit-ups are contraindicated due to the risk of increasing blood pressure and rupture [1, 2].
- *Depression and anxiety:* Patients with depression and anxiety may have higher dyspnea and lower adherence to PR; however, they have significant benefits with the program. For this reason, they should not be excluded from PR [1, 2].
- *Dyspnea:* PR has significant benefits in patients with chronic pulmonary diseases, whether they have dyspnea only with moderate intensity exercise [modified British Medical Research Council (mMRC) grade 2] or with daily life activities (mMRC grade 4). These patients with severe dyspnea, too breathless to leave their home, may also have significant benefit from domiciliary PR [1, 2].
- *Bronchodilator treatment:* Patients with chronic pulmonary disease need to be adequately treated prior to referral to a PR program. Bronchodilators decrease exertional dyspnea and dynamic hyperinflation and allow for better exercise tolerance and benefits from training [1, 2].

22.2.5 What Is the Ideal Duration and Frequency of a Pulmonary Rehabilitation Program?

Available evidence is insufficient to show the optimal duration of PR programs. However, a program duration of at least 8 weeks is recommended to attain a substantial effect. Most programs last 6–12 weeks. Studies with a duration less than 6 weeks have different designs and neither be compared nor be recommended. PR programs lasting longer than 12 weeks have documented greater benefits, including walk tests and stair climbing; however, the cost-effectiveness needs to be clarified before any recommendation [1, 2].

The optimal frequency of PR sessions remains unclear. However, studies have demonstrated a minimum of two weekly supervised sessions to show improvements in health status and quality of life. Also, patients should be encouraged to have a healthy lifestyle and maintain regular physical activity (30-min sessions, 5 times a week) [1, 2].

22.2.6 What Type of Physical Training Does Pulmonary Rehabilitation Include?

Individually tailored exercise training is considered the cornerstone of PR. These programs should include a combination of exercise endurance and resistance training, in order to achieve the best results, including greater peripheral muscle strength and balance compared to aerobic exercise alone [1, 2].

Aerobic training includes walking or cycling and, although the optimal intensity is not known, it is recommended a minimum target intensity of 60% of patient's predetermined peak work rate during at least a continuous period of 20 min, each session [1, 2, 10].

Not all patients with COPD are able to exercise for this period. Therefore, many other exercise training modalities and settings have been studied, ranging from Nordic walking for COPD patients with a relatively preserved exercise tolerance to neuromuscular electrical stimulation (NMES) for the most dyspneic, weakened, and perhaps even mechanically ventilated patients with COPD. Even though multiple training modalities and settings are available, a true personalization of the exercise training based on the pre-rehabilitation assessment is mostly lacking. A one-size-fits-all approach is a common practice [10].

Resistance training should target major muscles at 70–80% of the one repetition maximum (1RM) and include 2–4 sets of 8–12 repetitions each exercise. Weights should be progressively increased according with the patient capacity, and a minimum of 48 h rest is advised [1, 2, 11].

Ratings of perceived exertion (RPE) of 5–6 of 10 (moderate) and 7–8 of 10 (vigorous) may be used to help guide intensity during exercise training [10].

For weakened COPD patients with (very) severe dyspnea, resistance training may still be too burdensome to the impaired ventilator system, and NMES can be considered a substitute for resistance training [10].

PR may include interval (high intensity exercise interspersed with rest or low intensity exercise) or continuous training, depending on the patients' characteristics, since both strategies have the same results [1, 2].

Randomized controlled trials evidenced that individualized targeted exercise program had similar results compared with conventional PR [1, 2].

22.2.7 What Is the Role of Education in Pulmonary Rehabilitation Program?

Education is a major component of PR that aims to help patients control their disease and adopt a healthy lifestyle. It should include the following components [1, 2]:

- Basic concepts of the respiratory system anatomy and function.
- The importance of adopting a healthy lifestyle, particularly smoking cessation.
- The importance of physical exercise.
- The importance of their medication, how and when to use it.
- Management and recognition of symptoms and exacerbations.
- Anxiety and dyspnea management and relaxation techniques.
- Airway clearing techniques.
- Nutritional counselling.
- Psycho-social support.
- Sexuality.
- Self-efficacy and self-management.

22.2.8 Where Should Pulmonary Rehabilitation Take Place?

Most PR programs are hospital-based, with direct supervision of healthcare professionals [1, 2].

Home-based PR have shown similar benefits in some studies (walking distance), but certain conditions must be considered, including careful selection of patients, mechanisms of education and supervision, home equipment, and technology resources [2]. Although more convenient for the patient, home-based PR has the disadvantages of lacking group support, healthcare permanent supervision, equipment and facilities requirements, and the costs of periodical healthcare professionals' visits [3].

PR may also be considered in patients hospitalized in intensive care units, in order to reduce the disability associated with prolonged length of staying, respiratory failure, and muscle weakness [3].

22.2.9 Is Pulmonary Rehabilitation Safe after an Acute Exacerbation of the Disease?

The majority of studies includes patients integrated in a PR program in a stable phase of their disease. A Cochrane Review analyzed studies

including COPD patients referred to early PR (commencing within 1 month after hospital discharge due to an exacerbation). The results showed that early PR, when compared with usual care, has no higher risks of adverse events or mortality and has the advantage of improving quality of life and exercise capacity and reducing short-term risk of hospital readmission. For these reasons, patients should be offered early PR after an acute exacerbation of COPD [1–4].

22.2.10 What Is the Role of Adjuncts in Pulmonary Rehabilitation?

Inspiratory muscle training (IMT): IMT includes two types of training:

- Inspiratory resistive training, which consists of inhaling through a device against a threshold resistance.
- Normocapnic hyperpnea, which consists of periods of rapid breathing and deep inhalation of a controlled gas mixture that ensures normocapnia.

IMT is a safe and well-tolerated strategy that improves respiratory muscle strength and endurance. However, due to the lack of studies and their limitations, currently it is not recommended as a routine adjunct to PR [1, 2].

Hormones and nutritional supplements: Underweight COPD patients have worse prognosis compared with other patients. Different studies using nutritional supplements (protein, carbohydrates, fat, L-carnitine, amino acids, and creatine) and hormones (anabolic steroids) have several limitations, failed at improving exercise performance and cannot be recommended as a routine adjunct, although it may be considered on an individual basis [1, 2].

Noninvasive ventilation (NIV): Studies with NIV use in PR have reported improvements in exercise performance, but with no significant difference in walk distance, compared with standard PR alone. Currently, it is recommended that patients already using domiciliary NIV due to chronic respiratory failure may use NIV during PR, if tolerable. However, if a patient does not have indication for long-term NIV, it should not be offered to perform PR with the only goal of improving its outcomes [2, 11]. In hospitalized patients with acute exacerbation of their chronic pulmonary disease, the use of NIV may improve exercise tolerance and decrease oxygen desaturation [12].

Supplemental oxygen: In COPD patients who desaturate with exercise ($\leq$ 88%), the use of supplemental oxygen therapy is safe and may help increase exercise capacity and therefore the benefits of PR [9]. Advantages of this therapy are not well documented in other patients, and so, supplemental oxygen is not routinely advised in PR. In patients already receiving long-term oxygen therapy, PR may be a useful opportunity to adjust and review the prescription [1, 2]. To prevent exercise-induced oxygen desaturation, interval training should be considered [10].

Supplemental heliox: Heliox consists in a gas mixture of oxygen and helium (usually 21% and 79%, respectively) that provides a more laminar flow of oxygen, decreasing airway resistance and consequently, the work of breathing. However, its use in obstructive pulmonary diseases is controversial, since it may exacerbate small airways collapse. Studies including heliox in PR do not seem to increase the benefits of PR, and it should not be routinely used, unless there are conditions that require its administration (large airway obstruction or vocal cords dysfunction) [1, 2].

Neuromuscular electrical stimulation (NMES): NMES should not be routinely used in PR. However, selected patients with low body mass index, severe ventilatory limitation, and muscle wasting, who are unable to perform a regular PR program, may be candidates for NMES training, especially with expertise personnel [1, 2].

22.2.11 Is Technology a Useful Resource in Pulmonary Rehabilitation?

Telemedicine may be a useful strategy in the supervision of selected patients undergoing home-based PR, especially when they have diffi-

culties in the access to a hospital-based program. However, there are still scarce studies using technology as an adjunct of PR allowing safe recommendations [1, 2].

22.2.12 Should a Pulmonary Rehabilitation Program be Repeated?

The benefits of PR seem to persist for at least a year, and then gradually decline to the baseline of patient, although this may be variable. For this reason, PR may be repeated after a year of completion of the program, especially if the patient had benefited the first time [1–4]. Earlier referral may be considered in patients with exacerbations or rapid decline of pulmonary function [1, 2].

In order to maintain the benefits of a PR program, patients should be encouraged to maintain a healthy lifestyle and physical activity [1, 2].

22.2.13 What Else Can be Done to Improve Accessibility to Pulmonary Rehabilitation?

There are still many barriers in order to make PR an opportunity to every eligible patient. Both healthcare professionals and patients need to be more aware of the benefits of PR in order to improve referral and adherence to the program, respectively. Many patients lack access to PR (long distance, lack of transportation) and the majority of institutions lack resources. Also, many countries lack PR programs. Institutions need significant more funding and investment, and their structure needs to facilitate referral processes and access to the programs. National policies need to change and to improve conditions of patients and healthcare professionals [4].

The progressive use and implementation of tele-PR is a potential tool that may help reduce many limitations of PR, but studies are still lacking [4].

22.3 Conclusions

PR is one of the most important and cost-effective treatment strategies in the management of chronic pulmonary patients, promoting exercise tolerance, control of symptoms and disease outcomes, and HRQoL, and reducing healthcare need and costs. However, PR remains significantly underutilized worldwide.

Key Major Recommendations

- PR is one of the most important and cost-effective treatment strategies of chronic pulmonary patients.
- PR promotes exercise tolerance, HRQoL, symptoms, and disease control and reduces healthcare need and costs.
- PR remains significantly underutilized worldwide.
- Healthcare professionals need to be more aware of the benefits of PR in order to improve referral to the program.
- Tele-PR is a potential tool that may help reduce many limitations of PR.

References

1. McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015;2
2. Bolton C, Bevan-Smith E, Blakey J, et al. BTS guideline on pulmonary rehabilitation in adults. Thorax. 2013;68(2):ii1–ii30.
3. Gibson G, Loddenkemper R, Lundbäck B, et al. Respiratory health and disease in Europe: the new European Lung White Book. Eur Respir J. 2013;42:340–7.
4. Rochester C, Vogiatzis I, Holland A, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. Am J Respir Crit Care Med. 2015;192(11):1373–86.
5. Spruit M, Singh S, Garvey C, et al. An Official American Thoracic Society/European Respiratory Society Statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crt Care Med. 2015;188(8):e13–64.
6. Dreher M, Ekkernkamp E, Schmoor C, et al. Pulmonary rehabilitation and noninvasive ventilation in patients with hypercapnic interstitial lung disease. Respiration. 2015;89:208–13.

7. Rochester C, Fairburn C, Crouch R. Pulmonary rehabilitation for respiratory disorders other than chronic obstructive pulmonary disease. Clin Chest Med. 2014;35:369–89.
8. Young J, Jordan RE, Adab P, et al. Interventions to promote referral, uptake and adherence to pulmonary rehabilitation for people with chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2017;10
9. Garvey C, Bayles M, Hamm L, et al. Pulmonary rehabilitation exercise prescription in chronic obstructive pulmonary disease: review of selected guidelines—An official statement from the American Association of Cardiovascular and Pulmonary Rehabilitation. J Cardiopulm Rehabil Prev. 2016;36:75–83.
10. Woutersa E, Posthuma R, Koopman M, et al. An update on pulmonary rehabilitation techniques for patients with chronic obstructive pulmonary disease. Expert Rev Respir Med. 2020;14(2):149–61.
11. Ambrosino N, Cigni P. Non invasive ventilation as an additional tool for exercise training. Multidiscip Respir Med. 2015;10:14.
12. Dyer F, Flude L, Bazari F, et al. Non-invasive ventilation (NIV) as an aid to rehabilitation in acute respiratory disease. BMC Pulm Med. 2011;11:58.

Full Title: High-Risk Population, Elderly and Chronic Critically Ill Patients

23

Milly Bitzani and Evangelos Kaimakamis

Abstract

NIV is an effective alternative for elderly people requiring ventilator support for acute cardiorespiratory failure or during weaning in chronic critically ill patients. Its success is dependent on various factors. Several prognostic factors should be taken into consideration when applying NIV to post-extubation chronic critically ill patients, a specific group of patients requiring a holistic approach in their management.

Keywords

Chronic critically ill · Elderly · Exacerbation of COPD · Lung injury · NIV · Palliative care

Abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II
ARF	Acute respiratory failure
CHF	Chronic heart failure
DNI	Do not intubate
ETI	Endo-tracheal intubation
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation
RCT	Randomized control trial
RICU	Respiratory intensive care unit
SOFA	Sequential Organ Failure Assessment
VT	Tidal volume

23.1 Introduction

Although noninvasive mechanical ventilation (NIV) has been shown to play a key role in the management of acute respiratory failure (ARF), clear evidence is lacking about its utility in elderly or frail population and especially in the context of chronic critical illness. With growing numbers of elderly people being hospitalized in critical care settings, and many of them evolving to chronic critically ill patients, the alternative of NIV is a viable and potentially effective solution for their initial therapeutic approach as well as for facilitating their weaning from invasive mechanical ventilation. Current evidence and best practices on this subject are presented in this chapter.

M. Bitzani · E. Kaimakamis (✉)
1st ICU, "G. Papanikolaou" General Hospital, Thessaloniki, Greece

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_23

23.2 Discussion and Analysis of the Main Topic

23.2.1 High-Risk and Elderly Population

With the increase in life expectancy, the proportion of advanced age patients admitted to intensive care units is growing. According to recent epidemiological data, very old people account for 10–15% of ICU admissions. Acute respiratory failure (ARF) is one of the most frequent reasons for hospitalization, mainly due to cardiopulmonary diseases, with nearly 50% of admissions needing mechanical ventilation support. The use of invasive mechanical ventilation (IMV) in elderly patients decreased significantly over time, whereas NIV became gradually a primary therapeutic option. Although it initially focused, almost exclusively, in patients with acute COPD exacerbations, its use as a first-line supportive therapy to other respiratory and neuromuscular conditions is continuously increasing. NIV is aiming to prevent complications related to endotracheal intubation (ETI) and long-term sedation, whose incidence rate and severity are particularly high in fragile patients. Since the likelihood of death in adults requiring mechanical ventilation increases significantly with age, avoiding invasive procedures seems to be crucial in the elderly.

On the other hand, albeit the number of elderly patients meeting the criteria for mechanical ventilation is increasing, there is a tendency for elderly patients to be offered less invasive and costly treatment.

Furthermore, NIV has been proposed for the prevention of post-extubation failure in at-risk patients, as well as a "ceiling/rescue" therapy for patients on do-not-intubate (DNI) orders. Recently, the use of NIV as a palliative care, for patients with acute respiratory failure near the end of life, although debatable, gained some consideration.

Several studies showed increasing use of NIV with advancing of age. A recent study by Ugurlu et al. showed that NIV utilization rate, as a first-line ventilator treatment, was more frequent in patients ≥65y (49% and 47% for elderly and aged patients vs. 22% and 34% in young and middle aged). Moreover, NIV success and in-hospital mortality rates were similar among the different age groups [1]. Similar results are reported by Benhamou et al., who found a more frequent use of NIV in elderly than in younger patients (64% vs 47%) admitted in ICU for ARF. According to the same authors, NIV significantly reduced the rate of meeting intubation criteria (7.3% vs. 64.4%). Schortgen et al. reported NIV use in 60% of octogenarians requiring ventilator support [2].

The BTS Adult NIV Audit 2019, which included 3052 patients—mean age 72 y (64–80)—selected according to evidence base for NIV, found that NIV was successful in resolving respiratory acidemia in 76% of treated patients, with inpatient mortality 26%, which was the first reduced inpatient mortality reported since Audit 2010 [3].

According to evidence-based medicine and expert opinion, in patients with acute-on-chronic respiratory failure, cardiogenic pulmonary edema, or de novo ARF, the use of NIV reduces mortality, improves outcome, and represents an effective alternative of IMV for elderly patients needing respiratory support.

In addition to patients with ARF with no preset limitations on life-sustaining treatments, the Task Force on the "Palliation Use of NIV" of the Society of Critical Care Medicine recognized two more categories for patients to whom NIV treatment might be an adequate option:

- Life support when patients and families have decided to forego endotracheal intubation (ETI).
- As a palliative measure when patients and families have chosen to forego all life support, receiving only comfort measures.

The rate of do-not-intubate (DNI) orders has increased over time. The decision is usually guided by the patient's preference for no intubation, physician's belief that intubation would be of no therapeutic benefit/inappropriate, or by the lack of resource availability. DNI orders may occur at any point during a patient's clinical

course either in outpatient or inpatient settings. Risk of death is five times greater for patients with DNI orders.

DNI orders are more common in very old (>80 y) than in younger patients (40% vs. 8%). Although DNI cannot be considered an indication for NIV, patients with DNI orders are good candidates, in case of ARF. In a recent study by Wilson et al., one in four patients on NIV, due to ARF, had a do-not-intubate order [4]. In an RCT contacted by Nava et al., NIV was implemented as a rescue therapy to almost 53% of DNI patients (>75y) and was proved successful to 75% of them. Mortality rate was lower, in comparison to patients treated invasively and comparable to the overall NIV group [5]. More recent studies report similar results highlighting the importance of NIV as an alternative ventilatory tool in case ETI is neglected by the patient or questioned by the physician. This is particularly true for elderly to whom invasive treatments are often considered inappropriate or costly.

The third category includes patients with end-stage COPD, CHF, neuromuscular diseases, or terminal malignancy, with very poor baseline quality of life. In these cases, NIV must not be used as a life-prolonging therapy but as a tool for palliation of symptoms near the end of life. Whether the use of NIV is appropriate in this patient category is an ethical dilemma. Some authors suggest that is beneficial to symptoms' relief—especially dyspnea—and the facilitation of communication, during the dying process, while others consider that the tight-fitted face mask induce, by itself, discomfort to the patients and limits communication. In any case, the goals of this "time-limited" trial must be extensively discussed with patients and relatives, while patients must be encouraged to withdraw the treatment, if they cannot tolerate imposed discomfort. A careful patient selection is warranted (i.e., exclude unconscious patients). It would be interesting to investigate whether NIV is as effective in palliative care as pharmacological therapies. Nava et al. reported reduction of dyspnea and opiates dosage in patients with end-stage solid cancer.

The success of an NIV trial depends on various factors:

Setting: Inpatient mortality between patients who started NIV in a non-designated NIV respiratory ward area and those who started NIV in a designated respiratory ward area was reported significally different (40% vs. 29%) [3]. Depending on hospital policies, NIV-designated areas comprise respiratory ward, ICU, respiratory intensive care unit (RICU), emergency department, or any other high dependency unit. These are premises that ensure adequate equipment and are staffed by personnel—both medical and nursing—expert on NIV, provide cover 24/24 h, multi-parameter monitoring, prompt availability for ETI, and have a clear discharge protocol plan. ICU is an expensive and distressing environment that, although fits all these criteria, is not considered an ideal place to start NIV in less severe elderly with no other organ dysfunction. Instead, RICUs can provide specialized care, with lower nurse-to-patient ratio, reserve patients' privacy, and be more accessible to relatives, on top of being less expensive.

The choice of the setting for NIV to start depends on patients' condition, the assumed time response to NIV, the monitoring needs, and the goals set by the physician. Patients who are expected to poorly respond to NIV must be treated in ICU, with the exception of patients with DNI, or when it is applied for palliative reasons. All other cases can be treated in NIV designated areas outside ICU [6].

Time: Providing the physician has clearly defined the goals of the treatment for every single patient, NIV must start early, in order to prevent further deterioration.

The Device: There is a vast selection of high-performance devices, providing both ventilation and monitoring. The adequacy of a device is determined by its ability to maintain tidal volume (VT) stability by rapidly responding to leaks. Monitoring of VT, leakage, and minute ventilation is essential to assess NIV effectiveness. Most of the devices estimate these parameters through built-in software, but not all estimations are accurate. Other factors can also affect performance. Most of the devices—with single or double tube

circuit—fail to perform efficiently in the presence of true expiratory valve. Moreover, most built-in software fail to estimate leaks correctly when masks/interface used are not their own. Physicians should monitor these parameters carefully and be aware of these pitfalls while adjusting device settings according to software displayed values. So far, the best option for NIV configuration to unintentional leak compensation and accurate estimation of VT is a single limb circuit, with an intentional leak [7].

Patient selection: Age is not a contraindication. The type of acute respiratory decompensation must be defined carefully. Patients with hypercapnic acute respiratory failure are good responders to NIV, while patients with hypoxemic ARF are less responsive. Patients with neuromuscular diseases leading to pump failure are considered good candidates. On the contrary, in presence of encephalopathy, with the exception of hypercapnic, the application of NIV is contraindicated. Relative contraindications are secretions' retention, cough depression, and agitation/delirium. Moreover, severe acidosis (pH $\leq$ 7.25), de novo severe hypoxemia, and concomitant other organ failures increase the likelihood of NIV failure.

23.2.2 Chronic Critically Ill Patients

Recent advances in intensive care have enabled more patients to survive acute critical conditions, like acute cardiorespiratory failure. They also have created a large and growing population of chronic critically ill patients with prolonged dependence on mechanical ventilation and other intensive care interventions. This condition is considered present when the ICU length of stay exceeds the tenth day accompanied by invasive mechanical ventilation for more than 6 hours a day or a tracheostomy has been performed. Chronic critical illness is a devastating condition: mortality exceeds that for most malignancies, and functional dependence persists for most survivors. The cost of its treatment exceeds the spectrum of billion dollars every year worldwide and is continuously increasing [8]. The syndrome of chronic critical illness is a complex clinical entity. Most chronic critically ill patients are older adults who have underlying comorbid conditions and develop sepsis and other acute comorbidities with treatment for acute medical, surgical, neurologic, or cardiac critical illness. Beyond the hallmark of prolonged ventilator dependence, increasing evidence indicates that chronic critical illness is a syndrome affecting multiple systems and organs, with high morbidity and mortality.

The use of NIV in ARF has increased steadily over the period of the last 20 years. Its use has been associated with more favorable outcomes in selected patients admitted to intensive care units, with its use being a recommendation in certain patients. Mainly patients with acute hypercapnic respiratory failure or acute cardiologic decompensation are considered eligible for NIV, unless the PO_2/FiO_2 ratio is below 150 mmHg [9].

First-line NIV was associated with better 60-day survival and fewer ICU-acquired infections compared to first-line intubation in a multicentric study by Schnell et al. [10] The researchers studied 3163 patients, of whom 1232 (39%) received NIV. The latter decreased 60-day mortality [adjusted hazard ratio (aHR) = 0.75; 95% confidence interval (95% CI), 0.68–0.83; $p < 0.0001$]. On the other hand, NIV failure was an independent time-dependent risk factor for mortality (aHR = 4.2; 95% CI, 2.8–6.2; $p < 0.0001$). The research showed that survival benefits from NIV occurred only in patients with acute-on-chronic respiratory failure and immunocompromised patients.

Certain prognostic factors for successful noninvasive ventilation in acute hypoxemic respiratory failure can be used as a reference for physicians who treat high-risk patients with NIV. These prognostic factors with their characterization as favorable or adverse are summarized below:

23.2.2.1 Cause of Acute Hypoxemic Respiratory Failure

- Favorable: cardiogenic pulmonary edema, postoperative, and $PaO_2/FiO_2 > 200$ mmHg.
- Adverse: $PaO_2/FiO_2 < 200$ or 150 mmHg.

23.2.2.2 Predictors of Failure

- $PaO_2/FiO_2 < 150$ mmHg.
- Tidal volume (exhaled) under noninvasive ventilation (NIV) ≥9.0 or 9.5 mL/kg.
- High severity score (e.g., APACHE II or Sequential Organ Failure Assessment Score—SOFA).
- Heart rate, acidosis, consciousness, oxygenation, respiratory rate score (HACOR) >5 after 1 h of NIV.

In any case, delaying intubation must be avoided, especially in the presence of the aforementioned risk factors. Moreover, for patients with $PaO_2/FiO_2 < 200$ mmHg, a trial of high-flow oxygen with a nasal cannula is recommended as an alternative to NIV.

Concerning the contribution of NIV to a successful weaning from mechanical ventilation after prolonged use of the ventilator, it can be stated that it is a viable option for chronic critically ill patients. In this context, it is important to recognize physiological parameters that are able to predict the success of the NIV use and guide further therapeutic options. In 2016, Sancho et al. [11] published a paper which described their observations on the facilitation of weaning process with the aid of NIV. According to their findings, 85.71% of their patients achieved weaning success (mean weaning time from IMV 25.45 ± 16.71 days), of whom 21.4% needed NIV during the weaning process. The variable which predicted the need for NIV was arterial carbon dioxide tension at respiratory care unit admission (with OR = 1.08 (95% CI: 1.01–1.15), $p = 0.013$), with a cut-off point of 45.5 mmHg yielding sensitivity = 0.76, specificity = 0.67, positive predictive value = 0.76, and negative predictive value = 0.97. The authors concluded that NIV is a useful tool during weaning in chronic critically ill patients. An interesting fact is that hypercapnia despite mechanical ventilation at respiratory care unit admission was the main predictor of the need for NIV during weaning.

The monitoring of the pulmonary function in chronic critically ill patients exiting the ICU is problematic, as these patients have poor respiratory muscle functionality and their comorbidities profile, or the presence of tracheostomy, often prevents proper examination. Restrictive and obstructive patterns are both often present, whereas reduced vital capacity and altered functional residual capacity are common findings and mainly depict the severe muscle impairment. Therefore, it is mandatory to identify risk factors for early or late reintubation in patients under NIV sessions after prolonged IMV. The following are considered high-risk factors for reintubation:

- Age older than 65 years.
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score higher than 12 points on extubation day.
- Body mass index higher than 30.
- Inadequate secretions management.
- Difficult or prolonged weaning.
- More than 1 comorbidity.
- Heart failure as primary indication for mechanical ventilation.
- Moderate-to-severe chronic obstructive pulmonary disease.
- Airway patency problems.
- Prolonged mechanical ventilation.

In a related study, 19.1% of the patients treated with NIV after extubation were eventually reintubated [12]. Other researchers have shown that subjects with Sequential Organ Failure Assessment Score ≥ 5 had a higher risk of NIV failure in patients admitted to ICU for ARF associated with influenza virus infection. In cases that involve use of the ventilator of the ICU in an NIV mode, it is obviously easier to follow some monitoring information regarding the respiratory mechanics on the ventilator screen. The range of parameters are lim-

ited by the ventilator type and the availability of different modes of NIV by the ICU equipment. Observation of the respiratory curves (usually the flow, volume, and pressure values over time) is a useful method of assessing the patient's compliance, respiratory pattern, and possible dysynchrony with the ventilator, prompting corrective actions by the respiratory physician.

Another point of concern is the holistic management of ICU patients suffering from chronic critical illness. Apart from frequent need for NIV, these patients present difficulties in the cough function. Cough augmentation techniques like respiratory physiotherapy and mechanical cough assist devices can be used in parallel with NIV in high-risk cases. In addition, chronic critical illness causes an increase in energy expenditure, leading to proteolysis and related muscle loss. Careful supplementation and modulation of caloric and protein intake can avoid under- or overfeeding, which are both associated with poor outcomes. After weaning from the ventilator or during noninvasive ventilation, oral intake should be carefully evaluated and, in case of severe dysphagia, should be avoided and replaced by enteral of parenteral nutrition. Upon transfer from the ICU to the ward, adequate nutrition is essential for long-term rehabilitation. Continued and sufficient nutritional supplementation in the ward is necessary to avoid a suboptimal nutritional state [13].

Although the pool of chronic critically ill patients is constantly expanding, large RCTs studying the optimal use of NIV and its contraindications are still missing. The same applies for recommendations regarding monitoring of pulmonary function during NIV application. Further research is required toward this direction in order to define best practices for this fragile population.

23.3 Conclusion/Discussion

NIV is an effective alternative for elderly people requiring ventilator support for acute cardiorespiratory failure. The same applies for ventilatory support during weaning in chronic critically ill patients. Its success is dependent on various factors, like the setting where NIV is applied, its timely initiation, device specifications, and patient selection criteria. NIV can be used both as a palliative care for DNI patients and as a tool for weaning from IMV.

Several prognostic factors should be taken into consideration when applying NIV to post-extubation chronic critically ill patients. Older age, presence of comorbidities, high initial APACHE score, prolonged IMV or weaning process, COPD, problems in secretions management, and high BMI are some factors dictating potential failure in treatment with NIV in this category of patients. Cough augmentation and proper nutrition support are also crucial for chronic critically ill patients requiring NIV.

Further research is required toward definition of indications and pitfalls of NIV in chronic critical illness as well as recommendations for optimal cardiorespiratory monitoring during NIV in this fragile population.

Key Major Recommendations

- NIV is an effective alternative for elderly people requiring ventilator support for acute cardiorespiratory failure.
- NIV success in elderly subjects is dependent on factors like the setting of NIV application, the initiation time, the device used, and patient selection.
- NIV is a useful tool during weaning in chronically critically ill patients.
- Several prognostic factors should be taken into consideration when applying NIV to post-extubation chronic critically ill patients.
- Nutrition support is crucial for chronic critically ill patients requiring NIV.

References

1. Ugurlu A, Sldhom S, Kodabadeh A, et al. Use and outcome of NIV for acute respiratory failure in different age groups. Respir Care. 2016;61:36–43.
2. Schortgen F, Follin A, Piccari L, et al. Results of non invasive ventilation in very old patients. Ann Intensive Care. 2012;2:5.
3. BTS National Audit Report: Adult NIV Audit 2019. British Thoracic Society Reports. 2019;11:1–12.

4. Wilson M, Mittal A, Karki B, et al. Do – not – intubate orders in patients with acute respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2020;46:36–45.
5. Nava S, Grassi M, Fanfulla F, et al. Non invasive ventilation in elderly patients with hypercapnic respiratory failure: a randomized control trial. Age Aging. 2011;40:444–50.
6. Scala R. Challenges of non invasive ventilation to treat acute respiratory failure in the elderly. Pulm Med. 2016;16:150.
7. Lujan M, Lalmolda C, Ergan B. Basic concepts for tidal volume and leakage estimation in NIV. Turk Thorac. 2019;20:140–6.
8. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med. 2010;182:446–54.
9. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.
10. Schnell D, Timsit JF, Darmon M, et al. Noninvasive mechanical ventilation in acute respiratory failure: trends in use and outcomes. Intensive Care Med. 2014;40:582–91.
11. Sancho J, Servera E, Jara-Palomares L, et al. Noninvasive ventilation during the weaning process in chronically critically ill patients. ERJ Open Res. 2016;2:00061–2016.
12. Hernández G, Vaquero C, Colinas L, et al. Effect of Postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. JAMA. 2016;316:1565–74.
13. Singer P. Preserving the quality of life: nutrition in the ICU. Crit Care. 2019;23(Suppl 1):139.

Hypoxemic Respiratory Failure. VILI

24

R. D'Amico, A. Marra, M. Vargas, C. Iacovazzo, and G. Servillo

Abstract

Acute hypoxemic respiratory failure (AHRF) is severe arterial hypoxemia that is refractory to supplemental oxygen and could be caused by pneumonia, cardiogenic pulmonary edema, ARDS, and chronic obstructive pulmonary disease (COPD). ARDS is an important syndrome of noncardiogenic edema in which the most common risk factors include pneumonia, nonpulmonary sepsis, and aspiration (Stefan et al., J Hosp Med, 8:79–82, 2013).

Ventilator-induced lung injury is the acute lung injury inflicted or aggravated by mechanical ventilation during treatment and has the potential to cause significant morbidity and mortality. The predominant mechanisms by which the ventilator-induced lung injury occurs include alveolar overdistention (volutrauma), barotrauma, atelectotrauma, and inflammation (biotrauma).

Keywords

Acute hypoxemic respiratory failure
Ventilator-induced lung injury · Volutrauma
Barotrauma · Atelectrauma · Biotrauma

Abbreviations

AHRF	Acute hypoxemic respiratory failure
ALI	Acute lung injury
APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
CPAP	Continue positive airway pressure
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
HFOV	High-frequency oscillatory ventilation
HFPV	The high-frequency percussive ventilation
IPF	Idiopathic pulmonary fibrosis
P plat	Pressure of plateau
PE	Pulmonary embolism
PEEP	Positive end expiratory pressure
PFO	Patent foramen ovale
PP	Prone positioning
RCT	Randomized controlled study
VILI	Ventilator-induced lung injury

24.1 Introduction

Hypoxemia refers to low oxygen content in arterial blood, and there are several factors that impact this state: oxygen content of inspired gas,

R. D'Amico · A. Marra (✉) · M. Vargas
C. Iacovazzo · G. Servillo
Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_24

the matching of blood and alveolar gas, and amount of Hb in blood and its binding properties. Hypoxemia is defined as a partial pressure of oxygen of less than 80 mm Hg or arterial blood hemoglobin saturation of less than 95%.

The mechanisms of hypoxemia are as follows:

- Hypoventilation, as in narcotic overdose, head injury, airway obstruction, and neuromuscular weakness.
- Right-to-left shunt (anatomic or physiologic): PFO (patent foramen ovale), congenital cardiac disease, vascular malformations, atelectasis, pneumonia, and pulmonary edema.
- Ventilation/perfusion ratio mismatch: PE (pulmonary embolism) and COPD.
- Impaired diffusion: IPF (idiopathic pulmonary fibrosis).
- Low inspired oxygen: altitude.

24.1.1 VILI

Ventilator-induced lung injury (VILI) is an acute failure of pulmonary parenchyma caused by mechanical ventilation. It is characterized both by macroscopic damage that is pneumothorax and pneumomediastinum that represent the classic barotrauma and by microscopic injury like the alteration of alveolocapillary membrane, the degeneration of surfactant, and inflammatory modification very similar to the ones described in acute respiratory distress syndrome (ARDS).

The predominant mechanisms by which the ventilator-induced lung injury occurs include alveolar barotrauma, overdistention (volutrauma), atelectotrauma, and inflammation (biotrauma). Other mechanisms that are attributed include adverse heart-lung interactions, deflation related, and effort induced injuries. Related factors being studied in this context also include heterogeneous local lung mechanics, alveolar stress frequency, and stress failure of pulmonary capillaries. Variation in the expression of genetically determined inflammatory mediators has been known to affect VILI susceptibility [2].

Barotrauma is a pressure-related lung injury. It is defined as the presence of extraalveolar air in locations, where it is not normally found in patients receiving mechanical ventilation caused by high transpulmonary pressure. It may occur even at lower airway pressure if pleural pressure is very negative (e.g., forceful inspiratory effort). It includes pneumothorax and pneumomediastinum that can be found in lung X-ray in patients in high-pressure mechanical ventilation. Sometimes, there was also the presence of embolism above all in lower lung regions.

Volutrauma is lung injury caused by alveolar overdistension. It is caused by a ventilation based on high tidal volumes and high transpulmonary pressure.

Cyclical opening and closing of the atelectatic alveoli during the respiratory cycle could damage the adjacent non- atelectatic alveoli and airways by shear stress forces. This mechanism is called atelectotrauma. For atelectatic alveoli, high shear stress is generated during recruitment at the interface between the air bolus and collapsed airway, causing mechanical injury [3]. For flooded alveoli, formation and destruction of foam bubbles at the gas–liquid interface of flooded alveoli contribute additional local interfacial stress that disrupts plasma membrane–cytoskeletal adhesions and leads to lung injury [4]. The use of positive end expiratory pressure (PEEP) can prevent this damage because it avoids the continuous opening and collapse of alveolus, reducing also the inflammatory response associated with it. The application of optimal PEEP is important in the prevention of atelectrauma. Higher PEEP can cause alveolar overdistension, and lower PEEP may be inadequate to stabilize the alveoli and keep them open.

Biotrauma is the release of inflammatory mediators from the cells in the injured lungs in response to volutrauma and atelectotrauma. In ventilator-induced lung injury, the neutrophils, macrophages, and probably alveolar epithelial cells secrete various inflammatory mediators, including TNF-alpha, interleukins 6 & 8, transcription factor nuclear factor(NF)-kB, and matrix metalloproteinase-9. These cytokines could trigger detrimental effects locally and systemically, resulting in multiorgan failure.

24.2 Discussion and Analysis of the Main Topic

Given that mechanical ventilatory support with high volumes and pressures can cause preventable morbidity and mortality in critically ill patient, the first two mechanisms that were described at the basis of VILI were barotrauma and volutrauma. In fact, in 2000, the ARDS Network trial established that limiting tidal volume (6 vs. 12 ml/kg predicted body weight) and plateau airway pressure (</= 30 vs. </= 50 cmH_2O) brought a major survival in patients with ARDS.

The main cause of VILI is represented by transpulmonary pressure, which is the difference between alveolar pressure and pleural pressure, the difference between the pressure inside and the pressure outside the lung [3, 4].

There is a strong relation between transpulmonary pressure and tidal volume and a given lung volume produces a defined transpulmonary pressure. The alveoli are likened to balloon-like structures that stretch during insufflation of the tidal volume. In this phase, the alveolar walls seem to unfold so as to minimize this stretching up to the volume limit which corresponds to the total lung capacity. The stretching of the alveolar walls produces a rapid migration of lipids toward the plasma membranes so as to increase the cell surface and prevent its rupture [3, 5, 6].

When this inflammatory response is overwhelmed because a tidal volume greater than the total pulmonary capacity is insufflated, a systemic response and barrier damage with alveolar and interstitial edema, rupture of the joints and bubbles in the alveolar-capillary interstitium are triggered.

The other mechanism responsible for VILI is atelectrauma, which occurs through the cyclical opening and closing of the alveolar units. For atelectatic alveoli, shear forces that cause the mechanical damage come into play; in the edematous alveoli, on the other hand, air bubbles are formed and destroyed in the liquid–gas interface, which causes the destruction of the cellular junctions, at the basis of the microscopic lung damage. Low tidal volume ventilation may reduce the likelihood of atelectrauma because it avoids the exceeding of the critical opening pressure of the collapsed lung units. In addition, the role of PEEP is fundamental because of sustained recruitment and may prevent atelectrauma.

Finally, biotrauma is caused by an extensive biological response, including the activation of proinflammatory and proinjurious cytokine cascade that promote pulmonary and extrapulmonary organ injury. Epithelial surface area of adult lung is estimated to be 65–84 m^2; for this reason, the biological response undergoes an amplification mechanism as the entire volume of blood passes through the pulmonary filter with consequent damage at a systemic level and multiorgan failure syndrome.

Both the magnitude and frequency of peak alveolar stretch likely contribute to VILI in human studies, the use of infrequent high-volume breaths, like recruitment maneuvers, do not seem to cause lung injury, whereas the delivery of high tidal volumes with every breath worsens VILI and ARDS. For this reason, the right ventilation strategy of a patient with ARDS is to use low tidal volumes and high PEEPs.

There are risk scores that can be used to stratify the risk of developing a VILI: the lung injury prediction score (LIPS) and the early acute lung injury score. The first one is a score used to identify patients at risk for ARDS in the emergency department (ED). The second one is based on similar parameters:

- Oxygen requirement.
- Maximal respiratory rate.
- Baseline immune suppression.

These predictors accurately identify patients who can progress to acute lung injury requiring positive pressure ventilation (1 point for oxygen requirement >2–6 L/min or 2 points for >6 L/min; 1 point each for a respiratory rate ≥ 30 and immune suppression). An early acute lung injury score greater than or equal to 2 identified patients who progressed to acute lung injury with 89% sensitivity and 75% specificity.

Through these scores, patients at risk of developing lung damage from mechanical ventilation are identified but it is not possible to plan strategies to prevent the damage itself.

VILI prevention strategies in patients at risk include the following:

- Limitation of tidal volume (</ = 8 ml/kg PBW) in order to prevent volutrauma, decrease barotrauma, shear forces via smaller volume inflation of aerated alveoli adjacent to flooded/atelectatic alveoli and atelectrauma.
- Limitation of the inspiratory pressure to reduce the plateau pressure, the driving pressure or the transpulmonary pressure.
- Use a level of PEEP that maintains positive lung distending transpulmonary pressure at end-expiration leading to minimizing dependent collaps, but, at the same time, avoiding barotrauma.
- The use of prone position for at least 16 h to improve lung homogeneity and decrease shear forces.
- Respiratory rate limitation, to maintain either the lowest pH possible or the highest allowed $PaCO_2$. This strategy may require deep sedation, curarization, as well as extracorporeal CO_2 removal techniques.
- Limitation of respiratory effort through increased sedation and curarization to reduce expiratory effort and prevent cyclic derecruitment (atelectrauma).

The Berlin criteria categorize the severity of hypoxemia with a minimum positive end-expiratory pressure (PEEP) of 5 cmH_2O. On the basis of this definition, severe ARDS is defined as a PsO_2/FiO_2 </= 100 mmHg, moderate ARDS with a paO_2/FiO_2 between 100 mmHg and 200 mmHg, and mild ARDS with a PaO_2/FiO_2 >/= 200 mmHg. Several recent studies have focused on patients with ARDS in whom PaO_2/FiO_2 is <150 mmHg. This kind of ARDS is defined severe-moderate/severe ARDS, and it includes all patients most likely to respond to interventions such as prone positioning (PP) and neuromuscular blockade.

For patients suffering from severe respiratory failure volume-control and pressure-control modes are preferred, possibly associated with paralysis and deep sedation of the patient. The target tidal volume should be between 4 and 8 ml/kg predicted body weight and reduced to 4 ml/kg if the pressure of plateau (Pplat) exceeds 30 cmH_2O. In obese subjects, in abdominal hypertension, and in spinal deformities, conditions in which the chest wall exerts a collapsing effect on the lungs, it is safer to use a plateau pressure greater than 30 cmH_2O as long as an acceptable transpulmonary pressure is maintained. Gattinoni et al. [7] have suggested that the transpulmonary pressure should not exceed 22/23 cmH_2O since patients with ARDS suffer from a significant reduction of the lung parenchyma in which atelectatic areas are flanked by normally ventilated areas and, they can experience overdistension. For these reasons, patients with ARDS must receive protective mechanical ventilation with permissive hypercapnia. An important concept concerns the driving pressure mechanism which represents the difference between Pplat and PEEP.

Recent studies have correlated the driving pressure with patient outcome: the relative risk of death is >1 when the driving pressure > 15 cmH_2O.

24.2.1 Peep

The first step to optimize oxygenation and ventilation in patients with refractory hypoxemia is setting an optimal PEEP. In subjects with moderate and severe ARDS, hospital mortality was 34% with higher PEEPs and 39% with lower PEEPs. In subjects with mild ARDS, on the other hand, mortality was 27% with higher PEEP levels and 19% with lower levels. These data suggest that only patients with severe and moderate ARDS (P/F < 150 mmHg) benefit from higher end-expiratory pressures while those with mild ARDS do not derive any benefit from high PEEPs which can even be harmful.

Chiumello et al. [8] have shown that in the best PEEP trial, it is necessary to consider the changes in oxygenation reached after 5 min from the setting of a certain value of PEEP, while to evaluate the trend, it is necessary to wait 60 min or even more. The benefit of using PEEP in patients with refractory hypoxemia depends on the potential degree of alveolar recruitment. Gattinoni et al. [7] suggested that the same PEEP levels should be applied in patients with lungs with high and low recruitment potential and that choosing PEEP based on FiO_2 is the best choice. On the basis of the severity of

ARDS, the various levels of PEEP are set: 5–10 cmH_2O in mild ARDS, 10–15 cmH_2O in moderate ARDS, 15–20 cmH_2O in severe ARDS.

The choice of a PEEP suitable for the patient's respiratory mechanics is an essential aspect of proper ventilation. It is a balance between recruitment and overrelaxation. Goligher et al. [9] reported that an increase in P/F with an increase in PEEP is associated with a lower mortality, while a decrease in the P/F ratio after an increase in PEEP is associated with a higher mortality.

24.2.2 Recruitment Maneuvers

A recruitment maneuver is a transient increase in transpulmonary pressure in order to promote the reopening of collapsed alveoli, improving gas exchange and the distribution of volume in the lungs.

There are two possible approaches:

- Sustained high-pressure inflation using pressures of 30–40 cm H_2O for 30–40 s,
- A stepwise increase in PEEP with a constant Delta P or a fixed tidal volume.

Kenan et al., [10] suggested that stepwise recruitment maneuvers are more effective than abrupt applications of high peak pressure with less adverse hemodynamic effects.

One way to set the PEEP correctly is to perform a recruitment maneuver followed by a decreasing titration of the PEEP. The decremental titration is achieved by setting the positive pressure of finer expiration from 20 to 25 cmH_2O and then lowering it by 2 or 3 cmH_2O every 4/5 min. The correct level of PEEP is set to the value that can ensure good oxygenation and good compliance of the respiratory system.

There are also unconventional modes of ventilation used to treat refractory hypoxemic respiratory failure such as the high-frequency oscillatory ventilation (HFOV), the high-frequency percussive ventilation (HFPV), and airway pressure release ventilation (APRV).

HFOV delivers very low tidal volume (1–2 ml/kg) at high frequency (3–15 Hz/min). HFPV consists of pneumatically powered, pressure-limited, time-cycled, and flow-interrupted breaths with biphasic percussions. It generates pulses of subtidal volume that produce intrapulmonary percussive waves. These kinds of ventilation facilitate clearance of secretions, lung recruitment and reduce the need for sedation.

APRV applies CPAP (P high) for a prolonged time (T high) to maintain adequate lung volume and alveolar recruitment, with a time-cycled release phase to a lower set of pressure (P low) for a short period of time (T low) or (release time) where most of ventilation and CO_2 removal occurs.

24.2.3 ECMO

Extracorporeal membrane oxygenation, plays a crucial role in the management of acute hypoxemic respiratory failure. To perform standard respiratory ECMO, two vascular accesses are established, one for removal of venous blood and the other for infusion of oxygenated blood. Blood is drained from a major vein and pumped through a circuit that includes an oxygenator, which oxygenates the blood and removes carbon dioxide (CO_2), after which the oxygenated blood is returned via the other cannula. When blood is returned to the venous side of the circulation, the procedure is known as veno-venous ECMO (VV ECMO), which provides gas exchange but cannot give cardiac support. When blood is returned to the arterial side of the circulation, this is called veno-arterial ECMO (VA ECMO), and it can be employed for both gas exchange and cardiac support. Initiation of ECMO for adult ARDS should be considered when conventional therapy cannot maintain adequate oxygenation. Although there are no universally accepted criteria for ECMO initiation in ARDS, severe hypoxemia (PaO_2 to FiO_2 ratio < 80), uncompensated hypercapnia with acidemia (pH < 7.15), or excessively high end-inspiratory plateau pressures (>35–45 cm of water), despite standard of care ventilator management, have been proposed as reasonable indications for ECMO. ECMO can stabilize gas exchange and haemodynamic compromise, consequently preventing further hypoxic organ damage.

24.3 Conclusion Discussion

Treatment strategies for acute respiratory failure therefore include the use of a protective ventilation with low tidal volumes, high respiratory rates, and high PEEP values. This strategy allows to ventilate the hypoxemic patient by limiting the damage from pulmonary overdistension, which is responsible for barotrauma and volutrauma. The use of high positive pressure values at the end of expiration allows to recruit the alveoli, which would tend to collapse at the end of each respiratory cycle and to keep them open in order to avoid the formation of areas of atelectasis. The mode of ventilation that should preferably be used in these conditions is a mechanical ventilation with volume or pressure control that also limits the effort of the respiratory muscles. If the attempted controlled ventilation fails, additional strategies may be used including prone position, intermittent high-frequency ventilation, and ultimately, ECMO.

VILI is a pulmonary injury caused by mechanical ventilation. Its mechanisms are similar to those of ARDS because they recognize the same pathophysiology. In order to prevent barotrauma, atelectrauma, volutrauma and biotrauma, we use the same ventilatory strategy used for the treatment of ARDS. The goal of supportive therapy with artificial ventilation has changed over time, passing from normalization of plasma oxygenation and $PaCO_2$ values, at the cost of using high pressures or tidal volumes, to a ventilatory strategy based on the protection of the lung parenchyma in order to avoid alveolar overdistension and maintain its recruitment.

Key Major Recommendations

- VILI is a pulmonary damage caused by mechanical ventilation and multiple mechanisms have been described: barotrauma, volutrauma, atelectrauma, and biotrauma.
- VILI prevention strategies include limitation of tidal volume, use of PEEP, and limitation of the inspiratory pressure.
- PEEP is the first step to optimize oxygenation.
- Recruitment maneuvers consists of a transient increase in transpulmonary pressure that can reopen previously collapsed alveoli.
- ECMO provides an alternative to rescue patients with severe respiratory failure that conventional mechanical ventilation fails to maintain adequate gas exchange.

References

1. Stefan MS, Shieh MS, Pekow PS, et al. Epidemiology and outcomes of acute respiratory failure in the United States, 2001 to 2009: a national survey. J Hosp Med. 2013;8(2):76–82.
2. Hong SB, Huang Y, Moreno-Vinasco L, Sammani S, Moitra J, Barnard JW, Ma SF, Mirzapoiazova T, Evenoski C, Reeves RR, Chiang ET, Lang GD, Husain AN, Dudek SM, Jacobson JR, Ye SQ, Lussier YA, Garcia JG. Essential role of pre-B-cell colony enhancing factor in ventilator-induced lung injury. Am J Respir Crit Care Med. 2008;178(6):605–17.
3. Beitler JR, Malhotra A, Thompson BT. Ventilator-induced Lung Injury. Clin Chest Med. 2016;37(4):633–46. https://doi.org/10.1016/j.ccm.2016.07.004. Epub 2016 Oct 14. PMID: 27842744; PMCID: PMC5131805.
4. Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med. 1998;157:1721–5.
5. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol. 1970;28(5):596–608.
6. Talmor D, Sarge T, O'Donnell CR, et al. Esophageal and transpulmonary pressures in acute respiratory failure. Crit Care Med. 2006;34(5):1389–94.
7. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006;354:1775–86.
8. Chiumello D, Brioni M. Severe hypoxemia: which strategy to choose. Crit Care. 2016;20(1):132. https://doi.org/10.1186/s13054-016-1304-7. PMID: 27255913; PMCID: PMC4891828.
9. Goligher EC, Kavanagh BP, Rubenfeld GD, et al. Oxygenation 1182 response to positive end-expiratory pressure predicts mortality in 1183 acute respiratory distress syndrome. A secondary analysis of the 1184 LOVS and ExPress trials. Am J Respir Crit Care Med. 2014;190(1):70–6.
10. Marini JJ, Jaber S. Dynamic predictors of VILI risk: beyond the driving pressure. Intensive Care Med. 2016 Oct;42(10):1597-1600. https://doi.org/10.1007/s00134-016-4534-x. Epub 2016 Sep 16. PMID: 27637717.

Pulmonary Function-NIV. Cardiac, Thoracic, and Abdominal Surgery

25

André Cabrita, Bruno Cabrita, Gil Gonçalves, and Vanda Melo

Abstract

Postoperative pulmonary complications (PPCs) increase hospital length of stay, morbidity, and mortality in surgical patients. Perioperative noninvasive ventilation (NIV) may reduce the incidence of PPCs and should be considered, in a selected population, as a prophylactic and therapeutic tool to improve gas exchange. NIV demonstrated to be a better treatment than invasive ventilation in patients developing acute postoperative respiratory failure.

Keywords

Noninvasive ventilation · Cardiac surgery · Thoracic surgery · Abdominal surgery · Postoperative pulmonary complications

A. Cabrita (✉)
Cardiology Department at Centro Hospitalar São João, Porto, Portugal

B. Cabrita
Pulmonology Department at Hospital Pedro Hispano, Matosinhos, Portugal

G. Gonçalves
Pulmonology Department at Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

V. Melo
General and Family Medicine at USF Novos Rumos, Vizela, Portugal

Abbreviations

AAA	Abdominal aortic aneurysms
BPAP	Bilevel positive airway pressure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
MV	Mechanical ventilation
NIV	Noninvasive ventilation
OSA	Obstructive sleep apnea
PPC	Postoperative pulmonary complications
RCTs	Randomized controlled trials
VATS	Video-assisted thoracoscopic surgery

25.1 Introduction

Surgery can be associated with respiratory and cardiovascular complications, especially in high-risk patients. Maintenance of adequate perioperative respiratory function is mandatory for successful induction of anesthesia, execution of surgery, and recovery thereafter [1]. Hence, it is crucial to optimize a patient's physiological status in the preoperative period, provide lung protective ventilation in the intraoperative period, and extend optimal respiratory care into the postoperative period [2].

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_25

Invasive ventilation methods, such as reintubation and mechanical ventilation, have been the mainstay of treatment of postoperative respiratory failure, but they are associated with many complications [2]. The overall incidence of PPCs is quoted as 5–10% among all surgical patients and can be related to either complications of surgery or general anesthesia. PPCs can include atelectasis, postoperative pneumonia, pulmonary edema, and acute respiratory failure. It may adversely affect surgical morbidity and mortality and lead to an increased economic burden on healthcare systems [3].

NIV has been an established treatment in acute acidotic hypercapnic respiratory failure, caused by exacerbation of chronic obstructive pulmonary disease (COPD) or cardiogenic pulmonary edema, and as a facilitating tool for transitioning from invasive ventilation to spontaneous breathing. Nowadays NIV has also been used to prevent the occurrence of acute respiratory failure after surgery (prophylactic use) [3]. NIV has an important role in the prevention and treatment of PPC as it may prevent patient deterioration, reduce the incidence of hospital-acquired pneumonia, length of stay in critical care, need for invasive mechanical ventilation (IMV), and also confer mortality benefits in selected patient groups [1].

25.2 Discussion and Analysis of the Main Topic

25.2.1 NIV in Surgical Patients

NIV denotes administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy). Benefits of NIV include improvement in gas exchange, reduction of atelectasis, and work of breathing, while avoiding the complications associated with IMV. Hence, NIV has been adopted to prevent PPCs [1–3]. Compared to IMV, NIV is associated with improved patient comfort, reduced need for sedation, improved neurocognitive function, and a lower rate of nosocomial infections. Beside its advantages, NIV has some limitations, contraindications, and complications [1, 2]. NIV carries risk of patient-ventilator asynchronies, gastric distension, hemodynamic effects, and discomfort [4].

NIV in the perioperative period can be prophylactic or therapeutic. Prophylactic NIV aims to prevent the development of PPC. Therapeutic NIV is used in established respiratory compromise to prevent progression on to IMV and the associated detrimental sequelae [1, 2].

NIV can be recommended at any stage of the patient's perioperative journey. Preoperative continuous positive airway pressure (CPAP) may have beneficial effects on symptom severity and PPC in patients with obstructive sleep apnea (OSA). Intraoperative use of NIV is poorly investigated and clinical trials are required on this subject [4]. Intraoperative use of NIV along with neuraxial anesthesia may be justifiable in selected patients. NIV can partially compensate for the affected respiratory function by unloading the respiratory muscles and reducing the work of breathing, as well as improving alveolar recruitment with preservation of lung volumes, resulting in better gas exchange, reduce right ventricular preload and left ventricular afterload, and avoid complications of invasive mechanical ventilation [4]. However, NIV is most commonly used in the postoperative period, either due to the patient's comorbidities or after surgery carrying a high risk of PPC [1, 3]. The overall incidence of PPC is quoted up to 10% among all surgical patients and can be as high as 40% after abdominal surgery. PPC may adversely affect surgical morbidity and mortality and lead to an increased healthcare financial burden. Studies suggested that NIV was associated with a lower risk of acute respiratory failure after cardiac or thoracic surgery [5].

A clear mortality benefit with NIV usage in elective surgical populations has not been established, due to a relatively low baseline risk, although there may be survival benefits in selected high-risk patient groups [1].

25.2.2 Thoracic Surgery

Pulmonary complications remain the leading cause of death after thoracic surgery, occurring in 60–80% of patients [3]. NIV use after thoracic surgery has been demonstrated to be safe, without an increase in bronchial stump disruption and persistent air leaks. By requiring an intact respiratory drive, NIV may optimize the pulmonary ventilation to perfusion match, even better than in intubated patients, favoring the normalization of blood gas tension during the surgery, but with avoidance of intubation-related complications (trauma, airways mechanical irritation, infections). NIV improves gas exchange, reduces the need for IMV, and lowers mortality in patients with respiratory failure after lung resection [1, 5].

Evidence from thoracoabdominal aortic aneurysm repair suggests that prophylactic nasal CPAP reduces the incidence of pulmonary complications and leads to a shortened hospital length of stay. Also, patients with respiratory compromise after thoracoabdominal esophagogastrectomy have been shown to benefit from therapeutic NIV, with reductions in reintubation, septic shock, and critical care length of stay [1]. NIV also may alleviate acute respiratory failure secondary to blunt chest injuries. A recent meta-analysis suggested that NIV may lead to improved oxygenation, reduction in pulmonary complications, lower rate of intubation, and improved overall mortality [1].

Video-assisted thoracoscopic surgery (VATS) has been replacing the classical thoracotomy for several indications and the importance of this minimally invasive procedure has gradually increased. It represents an important element of enhanced recovery program in thoracic surgery. The goal is to minimize stress response, reduce postoperative pulmonary complications, and improve patient outcome [6]. A successful VATS under NIV in a terminal cancer patient with recurrent pleuro-pericardial effusion has been reported. NIV may facilitate the need to relieve symptoms due to recurrence of malignant pleural effusion without using endotracheal intubation, which may require postoperative ventilation [4].

25.2.3 Cardiac Surgery

Cardiac surgery can be accompanied by postoperative complications, which are associated with increased postoperative morbidity and mortality. Modern surgery techniques have been successful in decreasing adverse effects and both the operative and postoperative mortality [5]. Despite these good results, the incidence of postoperative morbidity is still significant [7]. PPC are the most common, with a prevalence ranging from 5% to 20% [5, 8]. Some authors reported that 40–90% of patients undergoing cardiac surgery have pulmonary complications [3]. Up to 10% of patients require a prolonged postoperative care, with longer intensive care unit (ICU) stays and worse long-term outcomes, which carries a higher healthcare cost. A meta-analysis suggests that early goal-directed hemodynamic therapy reduces postoperative complications and hospital length of stay after cardiac surgery, but no improvement in mortality has been found [7].

Few studies have demonstrated that NIV could improve the outcome of cardiothoracic patients with respiratory failure [9]. A randomized controlled study, comparing NIV with standard treatment, was negative in subjects with COPD after lung resection, although it improved oxygenation and pulmonary complications after cardiac surgery [9]. Compared to conventional management, NIV improved patient's oxygenation and decreased the need for endotracheal intubation, without significant complications, but did not demonstrate a significant effect on the risk of other outcomes [3, 5].

Obesity is a risk factor for postoperative hypoxemia after cardiac or thoracic surgery and prophylactic use of NIV is recommended in this specific population, in the postoperative period or after extubation, because it can unload the inspiratory muscles of obese patients [9].

A series of randomized controlled trials (RCTs) support the use of prophylactic nasal CPAP and demonstrated a reduction in PPC and need for critical care admission [1]. A meta-analysis suggested that prophylactic use of NIV reduced the rate of PPCs in patients after cardiac surgery. Prophylactic NIV could lower the rate of

atelectasis, reintubation, and other respiratory complications (pleural effusion, pneumonia, and hypoxia) [3, 8]. A mortality benefit has not been demonstrated with NIV therapy in elective surgical populations, probably due to a relatively low baseline risk. However, NIV has proven its benefits in prevention of PPC and reductions in critical care and hospital length of stay [1]. Although NIV was effective in the treatment of patients with postoperative acute respiratory failure, its role as a preventive tool, for PPC and need for IMV, remains unclear and is probably limited to high-risk patients [5].

25.2.4 Abdominal Surgery

Diaphragmatic dysfunction and severe reduction in vital capacity are among the most frequent complications of abdominal surgery and often lead to atelectasis and hypoxemia [2]. It has been reported that 9–40% of patients undergoing abdominal surgery developed at least one PPC [3]. Up to 50% of patients after abdominal surgery suffer from hypoxemia and 8–10% will ultimately require tracheal intubation. Current evidence suggests that both prophylactic and therapeutic use of CPAP may improve postoperative oxygenation, reduce atelectasis, decrease the incidence of pneumonia and rates of reintubation, and also reduce the length of ICU stay [1–3]. Among patients with hypoxemic respiratory failure following abdominal surgery, use of NIV, compared with standard oxygen therapy, reduced the risk of tracheal reintubation within 7 days, while fewer patients developed healthcare-associated infections, but there were no significant differences in gas exchange [10]. These findings could be explained by NIV effect on reducing atelectasis, which could decrease bacterial growth and mitigate bacterial translocation from the lung into the bloodstream. Furthermore, avoidance of endotracheal intubation is probably the major reason for the pneumonia reduction. In multiple RCTs, NIV has shown benefits in the treatment of respiratory failure of nonsurgical patients. However, no RCTs have evaluated whether NIV could reduce the need for IMV and its effect on the incidence of healthcare-associated infections in patients who develop hypoxemic acute respiratory failure after abdominal surgery [10].

Stock et al. reported that patients receiving CPAP after cholecystectomy had a significantly improved functional residual capacity and lesser evidence of atelectasis than those treated with kinesiotherapy [2]. Yurtlu et al. reported the successful application of NIV, together with epidural anesthesia, for emergency open cholecystectomy in a COPD patient with severe airflow obstruction and hypercapnic respiratory failure [4]. Squadarone et al. verified that CPAP use in patients who developed postoperative hypoxemia after laparotomy significantly reduced the incidence of endotracheal intubation and other severe complications [2]. Application of nasal CPAP after abdominal aortic aneurisms repair was found to result in significantly improved oxygenation and fewer episodes of severe hypoxia, but had no effect on rates of mortality, cardiac or respiratory complications, and length of stay [1].

In the largest prospective worldwide database on bariatric surgery, acute respiratory failure represented the fourth cause of mortality (11%). Current evidence has demonstrated clear benefits of prophylactic NIV in the postoperative period of abdominal surgery, in morbidly obese patients [3]. Joris et al. applied bilevel positive airway pressure (BPAP) in these patients, which significantly improved the peak expiratory flow rate, the forced vital capacity, and the oxygen saturation on the first postoperative day. The beneficial effects of NIV were attributed to an improvement in lung inflation, prevention of alveolar collapse, and reduced inspiratory threshold load [2].

Some studies have denoted complications with NIV use, including gastric distention and pulmonary aspiration [10]. There is concern about increased anastomotic leakage in patients treated with NIV after abdominal surgery. However, there have been several studies on the use of NIV in patients who had undergone proce-

dures like esophagectomies, digestive surgeries, gastrectomies, and colostomies showing increased benefits and reduced morbidity with use of NIV postoperatively [2].

25.3 Conclusion Discussion

Anesthesia and surgery can severely impair respiratory function, resulting in PPCs and respiratory failure. Despite the limited data and the need for more RCTs, NIV has proven to be an effective treatment, decreasing the need for invasive ventilation, in the setting of moderate to severe acute postoperative respiratory failure. Early administration of NIV should be considered both as a prophylactic and therapeutic tool in postoperative patients [3]. NIV improves the matching of ventilation to perfusion in the dependent lung areas and reduces respiratory muscles workload. These benefits are especially desirable in patients affected by restrictive or obstructive lung diseases [4]. Peri- and postoperative use of NIV has not only reduced intubation rates but has also reduced morbidity and hospital length of stay [2]. Clear mortality benefits from perioperative NIV are difficult to demonstrate but may be present in high-risk surgical patients. The optimal settings and duration of therapy remain unclear [1].

Key Major Recommendations

- NIV may reduce the incidence of postoperative complications.
- NIV should be considered both as prophylactic and therapeutic tool in postoperative patients.
- NIV has proven to be an effective treatment option, preventing the need for invasive ventilation.
- Mortality benefits from perioperative NIV have not been clearly proven.

References

1. Bauchmuller K, Glossop AJ. Non-invasive ventilation in the perioperative period. BJA Educ. 2016;16:299–304.
2. Mathai AS. Non-invasive ventilation in the postoperative period: is there a role? Indian J Anaesth. 2001;55:325–33.
3. Chiumello D, Chevallard G, Gregoretti C. Non-invasive ventilation in postoperative patients: a systematic review. Intensive Care Med. 2001;37:918–29.
4. Corcione N, et al. Non-invasive ventilation during surgery under neuraxial anaesthesia: a pathophysiological perspective on application and benefits and a systematic literature review. Anaesthesiol Intensive Ther. 2019;51:1–10.
5. Zhu G, Huang Y, Wei D, et al. Efficacy and safety of noninvasive ventilation in patients after cardiothoracic surgery. Medicine (Baltimore). 2016;95e:4734.
6. Dinic VD, et al. Enhanced recovery in thoracic surgery: a review. Front Med. 2018;5:1–7.
7. Aya HD, Cecconi M, Hamilton M, et al. Goal-directed therapy in cardiac surgery: a systematic review and meta-analysis. Br J Anaesth. 2013;110:510–7.
8. Liu Q, Shan M, Liu J, et al. Prophylactic noninvasive ventilation versus conventional care in patients after cardiac surgery. J Surg Res. 2020;246:384–94.
9. Stéphan F, Bérard L, Rézaiguia-Delclaux S, et al. High-flow nasal cannula therapy versus intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. Respir Care. 2017;62:1193–202.
10. Omar Bani-Saad. Potential indication for non-invasive ventilation following abdominal surgery. ESICM J, 2016

26 Pulmonary Function-NIV. Traumatic Cervical Spinal Cord Injury and Neurosurgery

Ertay Boran

Abstract

The spinal level of neurologic injury, the type of neurologic deficit, and the duration of injury are all factors that define the degree of respiratory impairment. Usually, functional compromise worsens as the level of injury is higher. Detailed monitoring must be applied in all patients with cervical spine injury and after neurosurgery for early detection of respiratory failure.

Keywords

Cervical spinal cord injury · Neurosurgery · Pulmonary function · Noninvasive ventilation

Abbreviations

COPD	Chronic obstructive pulmonary disease
CPP	Cerebral perfusion pressure
CSCI	Cervical spinal cord injury
FRC	Functional residual capacity
FVC	Forced vital capacity
GCS	Glasgow Coma Scale
GPB	Glossopharyngeal breathing
ICP	Intracranial pressure
ICU	Intensive care unit
NIV	Noninvasive ventilation
OSA	Obstructive sleep apnea
PEEP	Positive end-expiratory pressure
Pimax	Maximal inspiratory pressure
RV	Residual volume
SCI	Spinal cord injury
VC	Vital capacity

E. Boran (✉)
Faculty of Medicine, Department of Anesthesiology and Reanimation, Duzce University, Düzce, Turkey

26.1 Introduction

Motor vehicle accidents are the most frequent cause of cervical spine cord injury (CSCI), followed by falls, sports injuries, and gunshot or stab wounds. People experiencing head-first falls and unrestrained (by seat belts) drivers or passengers in high-speed, front-end motor vehicle accidents are at particularly high risk for CSCI [1].

Respiratory complications are one of the most common and serious clinical conditions in traumatic CSCI patients and are an important cause of morbidity and mortality also after neurosurgical operations [1].

The level of spinal cord injury (SCI) is a definite factor in ventilator dependence; 85% of C1 patients, 72% of C2, and 40% of C3 require mechanical ventilation [2].

Intensive pulmonary therapy initiated early after acute C1–C5 CSCI and after neurosurgery is associated with increased survival, decreased

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_26

incidence of pulmonary complications, and decreased need for ventilatory support [2, 3].

Primary pulmonary function evaluation and follow-up assessments are mandatory for early diagnosis of acute respiratory failure [3].

The use of noninvasive ventilation (NIV) for patients with high-level tetraplegia was first showed in 1990. It was reported that chronic SCI patients with tracheostomy tube could be extubated and managed by NIV. Largely, most patients with SCI and ventilatory insufficiency are suitable candidates for NIV [2].

There is little information on the clinical benefits and indications of NIV for CSCI and neurosurgery, especially the timing of introduction of NIV [2].

The aim of this study is to overview the pulmonary function and the NIV's clinical effectiveness in traumatic cervical spine injury and neurosurgery patients.

26.2 Discussion and Analysis of the Main Topic

26.2.1 Pulmonary Function After CSCI and Neurosurgery

Patients undergoing neurosurgical procedures experience a greater frequency of respiratory failure compared with other surgical specialties. Potential reasons for this increased risk include a higher incidence of altered mental status, prolonged surgical procedures, and central respiratory dysfunction secondary to postoperative swelling (i.e., retraction near the brain stem). Vital structures, such as the brain stem and cranial nerves, which are susceptible to compression, may be affected during surgery. Furthermore, intraoperative prone positioning may precipitate mechanical airway obstruction from macroglossia, whereas resection near the brain stem may produce central respiratory dysfunction and cranial nerve injury [4].

A decline in conscious level results in diminished airway reflexes. Generally, patients with a Glasgow Coma Scale (GCS) below 8 cannot protect their airways; similarly, those patients with lower cranial nerve dysfunction (e.g., after posterior fossa surgery) are at risk if laryngeal reflexes, cough, or swallow are diminished [5]. Intracranial hypertension is a risk factor for the development of neurogenic pulmonary edema.

Shortly after a traumatic SCI, there is a period of spinal shock lasting weeks and months, resulting in flaccid paralysis of muscles below the injury level. The flaccid paralysis of the intercostal muscles establishes an unstable thoracic wall such that negative intrathoracic pressure during inspiration causes paradoxical inward collapse of the ribs. This mechanical instability and disadvantage results in less effective ventilation, increased work of breathing, and a propensity toward distal airway collapse and microatelectasis. Airway secretions may accumulate in the bronchi and bronchioles through increased production or decreased clearance due to reduced coughing. During this period, the possibility of intubation and ventilation for respiratory support is high [6].

Over time and due to weakness, the active chest wall movement decreases, the tendons, ligaments, and joints of the rib cage harden. Together with spasticity of the intercostal muscles, the thoracic wall will be stabilized at a lower absolute lung volume. The resolution of spinal shock may also improve lung volumes as the thoracic and abdominal muscles begin to develop spasticity [6]. The respiratory failure risk is directly related to the level of injury. Trauma above C3 is reason to nearly complete respiratory muscle paralysis. These patients use the platysma, mylohyoid, sternohyoid, and trapezius muscles to support the sternocleidomastoid muscles with respiration. The situation becomes even more complicated when central alveolar hypoventilation developed. The automatic control of breathing is impaired by disrupting the reticulospinal pathways of the upper cervical cord (lesions ventrally located). Lesions located laterally protect the automatic control but weaken voluntary ventilation [7].

In injuries above C6, sympathetic innervation of the heart is disrupted and vagal tone with bradycardia increases. This may cause cardiac arrest during suctioning in intubated patients and

sometimes a temporary pacemaker may be required. According of the level of SCI, peripheral paralysis of the arms, legs, or both will occur, followed later by spasticity. The symptoms of upper SCI are dyspnea, which may be worsening in the sitting position, due to paralysis of respiratory muscles. Coughing is also damaged because the inspiratory phase of cough consists of a deep inspiration. Further, the expiratory muscles that participate to cough are also paralyzed. As a result, secretion blockage and development of atelectasis develop. Also, speech is affected and patients speak in a low voice. Lung function shows a restrictive pattern with reduced vital capacity (VC) and total lung capacity (TLC). Patients generally have rapid shallow breathing [6, 7]. The absent tone of the chest wall muscles results in a reduction of the chest wall recoil pressure [7]. C4–7 injury leads to a forced vital capacity (FVC) of 52% and a maximal inspiratory pressure (Pimax) of 64% predicted normal [6, 7].

The body position has a significantly high influence on lung function according to healthy subjects. Patients with cervical cord transection show an increase in VC and Pimax and a decrease in RV and FRC when moving from a sitting position to a supine posture. In the sitting position, the diaphragm is pulled down by the abdomen, but in the supine position, the abdomen moves the diaphragm upward. Furthermore, the loss of the intercostal muscle function may move the upper rib cage paradoxically inward during inspiration. Spinal cord injuries between C3 and C8 usually do not lead to ventilatory failure. But respiratory failure may develop more often with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], obesity, sleep apnea) [7].

Another complication of CSCI is nocturnal disordered breathing during the chronic stage. Irregular breathing, Cheyne-Stokes respiration, and both central and obstructive sleep apnea have been described in such patients [2]. These respiratory problems during sleep could worsen the ventilatory status and lead to daytime ventilatory impairment [2].

26.2.2 Physiologic Effects of NIV on Neurologic System

High positive end-expiratory pressure (PEEP) may induce an increase in intracranial pressure (ICP) through increasing central venous pressure. Also, the hemodynamic effects of high PEEP, as reduction of cardiac output and blood pressure, could produce critical reductions in cerebral perfusion pressure (CPP) and may lead to cerebral ischemia. NIV also leads to increase in ICP and lowers CPP, which has to be remembered when applying NIV to neurosurgery patients [8]. The hypoxemia that arises after CSCI may exacerbate spinal cord ischemia [3].

Both respiratory and central nervous systems are intimately interconnected through a delicate balance. Any disorder in this equilibrium can translate to devastating consequences for a patient [8].

26.2.3 Risk Factors for Postoperative Pulmonary Complications

Intraoperative blood loss and hypotension requiring transfusion and excessive IV fluids and prone positioning resulting in facial and airway edema which reduce lung compliance may further deteriorate patient's respiratory status. Therefore transfusion-related acute lung injury may develop [3].

The already affected airway reflexes, including cough and gag, may further lessen by the residual anesthetic agents and opioids. Therefore, these patients should be transferred to the ICU. Already patients with preoperative reasonable respiratory status may require postoperative mechanical ventilation. Patients with lesions of C5 and above are especially at risk for respiratory failure [3].

Risk factors for respiratory failure after neurosurgery include older age, longer procedure time, renal and pulmonary comorbidity, nonelective (emergency) surgery, preoperative alcohol use, functional dependence prior to surgery, operation type (cranial, infratentorial), high SCI, stroke, altered mental status, and central respiratory dys-

function secondary to postoperative swelling [4, 5, 9].

The spinal level of neurologic injury, the type of neurologic deficit, and the duration of injury are all factors that define the degree of respiratory impairment. Usually, functional compromise worsens as the level of injury is higher.

Respiratory complications following CSCI are poor coughing, increased airway secretions, and bronchospasm, which predispose to atelectasis, pneumonia, and exacerbations of respiratory failure [2].

Early surgical stabilization of the spine is typical practice in the majority of traumatic CSCI patients [6]. Patients are generally intubated for surgery, and once surgically stabilized they are admitted to intensive care postoperatively [6]. Because of acute respiratory insufficiency due to the spinal trauma the patient's intubation duration may be prolonged and followed by tracheostomy. The times of spontaneously breathing may be decreased by tracheostomy due to diaphragm deconditioning, tube-induced airway secretions, hyperventilation causing hypercapnea, inability to cough, and loss of glottis valving [7].

The major sleep-related respiratory problem post CSCI is obstructive sleep apnea (OSA). The OSA appears as a direct consequence of cervical injury and is up to 83% prevalent in the first year [6]. Neurocognitive impairments including decreased memory and attention have also been linked to nocturnal hypoxia in tetraplegic subjects with untreated OSA [6].

26.2.4 Benefits of NIV

NIV may be an important tool to prevent (prophylactic treatment) or treat (curative treatment) respiratory failure by avoiding intubation.

NIV could be indicated to prevent respiratory failure in high-risk patients, like patients affected by obesity, OSA, COPD, coronary artery disease, muscular dystrophy, or neurologic disease.

NIV can be a logical solution when curarization is not absolutely required. NIV can support the respiratory function, allowing maintenance of the correct position. Also, NIV can counterbalance the respiratory depression associated to sedative and local anesthetic agents [10].

NIV benefits can be summarized as: (1) to reduce the work of breathing; (2) to improve alveolar recruitment resulting in better gas exchange; and (3) to reduce left ventricular afterload, increasing cardiac output and improving hemodynamy [11].

Applying positive pressure can prevent atelectasis, reduce the severity of inflammatory pulmonary effusion, and improve cardiac function [10].

NIV is notified to decrease the complications of granulation formation, stomal infection, tracheomalacia, tracheal perforation, stenosis, fistula formation, decreased voice volume during long-term tracheostomy ventilation, and helps perform glossopharyngeal breathing (GPB) after CSCI [2].

Clinical improvement after the initiation of NIV within 1 year of CSCI can strengthen the sternocleidomastoid and trapezius muscles to expand the chest and enhanced voluntary ventilation and increased the ventilator-free time [2].

One of the major potential clinical benefits of NIV in CSCI patients was the increased force of the cough act, which facilitated the exhalation of thick sputum [2].

CSCI patients who used NIV with a mouthpiece were able to start spontaneous breathing safely and without assistance. They practiced voluntary ventilation with the continued use of NIV, which promoted ventilatory sufficiency and prevented fatigue. Strengthening of respiratory accessory muscles should be an important goal of NIV therapy [2].

In CSCI cases, compared with invasive ventilation, NIV improves quality of life, reduces nursing requirements and costs, improves the quality of speech, and is more effective in coughing. NIV also enables the ability of GPB, which

is a protection in the event of ventilatory equipment failure [7].

26.2.5 Complications of NIV

The serious complications associated with NIV in perioperative use are very uncommon. The most serious is the increase in mortality associated with late intubation when NIV fails. In most cases they are only mild complications that are conditioned by the type of interphase and patient-fan interaction, gas flow, and circuit pressurization [10]. The use of NIV in patients with high-level CSCI did not cause major clinical complications during a period of 2 years [2].

26.3 NIV in CSCI Patients

The time on NIV is often longer in patients with SCI compared with other diseases and lower inspiratory pressure is required [7]. The extensive time on NIV sometimes requires interfaces other than full face mask, and the use of a mouthpiece or a combination of different interfaces is common [7].

Setting up a daytime mode using a mouthpiece and a volume-controlled mode without PEEP followed by a night time mode using a nasal mask with a pressure-controlled mode with PEEP is one possible way to establish NIV in spinal cord paralysis [7].

Another major problem with high-level quadriplegia is decreased ability of coughing, which requires techniques to remove bronchial secretions like mechanically assisted coughing. This problem is not solved by intubation and invasive ventilation, and simple tracheal sucking does not prevent the incidence of atelectasis. Hereof, NIV is better than invasive ventilation, particularly when using specialized techniques like "air stacking." Air stacking permits voluntary sighing, shouting, and assisted coughing [7].

A different treatment option consists of electrophrenic nerve stimulation. For patients with no ventilator-free breathing ability or ability to grab a mouthpiece for NIV, electrophrenic pacing may be an alternative ventilator approach or may facilitate decannulation. Decannulation and applying NIV is generally possible with patients who have a functioning bulbar musculature [7]. The ability of neck rotation may also be a decision-making purpose in management of NIV, because it facilitates the use of a mouthpiece for ventilation [7].

Restoration of lung volume is the treatment goal of a person with acute tetraplegia or high paraplegia. Intermittent NIV via a mouthpiece or facemask to support inspiration prior to manually assist coughing can increase lung volume and exhalation flow [6].

High-level tetraplegic patients can be safely treated without invasive ventilation or tracheostomy in units with significant SCI and NIV practice. Early extubation and intensive physiotherapy may decrease the intensive care length of stay in suitable patients [6].

People with tetraplegia are much more likely to need NIV for OSA, but upper limb motor dysfunction, less independence in donning and removing masks, and increased need for caregiver support time make use difficult [6].

Neurological level for complete SCI, typical respiratory impairment, and support are summarized as:

- **C1–C3:** Likely full time, ventilator–dependent, secondary to severe diaphragm weakness (paralysis). May be able to come off ventilation for brief period if able to adequately self-ventilate using frog breathing/GPB. Potential candidate for diaphragm pacing.
- **C3–C4:** Diaphragm function will be impaired; reducing tidal volume and vital capacity. Periods of unassisted ventilation (ventilator-free time) are likely and may be adequately supported with nocturnal ventilation alone domiciliary ventilatory support may be noninvasive, particularly if lung volumes are high enough during day while seated.
- **C5:** Independent respiration is possible in long term, although common initial ventilatory support. Diaphragm function intact, but intercostal and abdominal muscle paralysis

results in decreased lung volumes and cough strength and effectiveness.

- **C6–8:** Independent breathing people with lesions caudal to C7 typically can augment inspiration and cough with accessory muscles, particularly pectoralis major and minor [6].

26.4 Intraoperative and Postoperative NIV

Intraoperative NIV was used uneventfully in anesthesia for awake craniotomy in selected high-risk patients to prevent ARF [10]. NIV also was applied successfully in the treatment of subarachnoid pleural fistulas [12].

Although severe encephalopathy (GCS <8) has been proposed as a possible contraindication to the use of NIV, some articles have shown its effectiveness in patients with altered state of consciousness or even coma secondary to respiratory failure [8]. In patients with hemorrhagic stroke, PEEP values up to 14 cmH_2O did not alter cerebral perfusion pressure or mean blood pressure [13].

CPAP and noninvasive nasal ventilation may be necessary in patients with reduced ventilatory capacity, but both modes of support are contraindicated if the neurosurgical wound involves the nasopharynx, with potential continuity with the intracranial space (e.g., after transsphenoidal surgery) [5].

Also to prevent the rise of intracranial pressure and decrease of the $PaCO_2$ levels which can cause the cerebral vasospasm, CPAP treatment must be carefully applied [14].

Effect of prophylactic insensitive spirometry and CPAP on respiratory functions after craniotomy was investigated and favorable effect of spirometry in neurosurgery patients was shown. Also, no side effect of CPAP of 10 cmH_2O was detected [14].

Whether routine or prophylactic NIV can prevent respiratory failure in neurosurgical patients is unknown. At present, there is no evidence supporting the effectiveness of NIV in patients undergoing craniotomy. Applying PPV to patients with intracranial lesions should be weighed carefully against the risk of increasing intracranial pressure or the risk of cerebral vasospasm with decreased $PaCO_2$ from NIV [12].

26.5 Patient Care

In neurosurgical patients, application of adequate PEEP should be applied under monitoring of mean arterial pressure, ICP, and CPP, as well as, ideally, some additional surrogate marker for cerebral perfusion [9].

Detailed monitoring must be applied in all patients with cervical spine injury for early detection of respiratory failure. Primary pulmonary function evaluation and follow-up assessments are mandatory for early diagnosis of acute respiratory failure [3].

ICUs with facilities for continuous monitoring of central venous pressure, arterial pressure, pulse, respiration rate and pattern, and oxygenation–perfusion parameters must be available for all patients with neurological injuries following acute SCI, particularly those injuries above the C6 level [3].

26.6 Conclusion Discussion

Respiratory impairment following SCI is more severe in high cervical injuries and is characterized by low lung volumes and a weak cough secondary to respiratory muscle weakness.

Postoperative lung expansion with incentive spirometry, chest physical therapy, postural drainage, and continuous positive airway pressure are useful for the prevention of atelectasies and pulmonary failure.

In high-level CSCI patients who are dependent on mechanical ventilation, introduction of NIV within 1 year of injury is recommended. Switching tracheostomy ventilation to NIV was proved safe and was associated with better clinical outcome [2]. NIV is superior compared with invasive ventilation concerning quality of life, nursing requirements and costs, effectiveness of coughing, and speech. The preferred devices for

NIV adaptation are the nasal mask, nasal pillows, and the mouthpiece, whereas full face and total face masks should be avoided.

Further research on NIV in CSCI and neurosurgical conditions can be conducted to extend the use of NIV.

Key Major Recommendations

- A trained team, careful patient selection, and optimal choice of devices can optimize outcome of NIV.
- NIV is the preferred approach to ventilation in patients with SCI. Special care has to be taken because of the patients' limb paralysis, which affects self-management of NIV and requires interfaces such as a mouthpiece.
- Every patient undergoing surgery should be clinically assessed for respiratory conditions.
- Respiratory impairment following SCI is more severe in high cervical injuries and is characterized by low lung volumes and a weak cough secondary to respiratory muscle weakness.
- The management following acute high cervical SCI is tracheostomy and ventilation, with NIV and assisted coughing techniques being important in lower cervical injuries.

References

1. Patel P, Cottrell JE. Spinal cord injury. In: Cottrell and Patel's neuroanesthesia. 6th ed. Elsevier; 2017. p. 177–85.
2. Toki A, Nakamura T, Nishimura Y, et al. Clinical introduction and benefits of non-invasive ventilation for above C3 cervical spinal cord injury. J Spinal Cord Med. 2019;12:1–7.
3. Prabhakar H. Spinal cord surgery. In: Essentials of neuroanesthesia. Academic Press; 2017. p. 567–78.
4. Flexman AM, Merriman B. Infratentorial neurosurgery is an independent risk factor for respiratory failure and death in patients undergoing intracranial tumor resection. J Neurosurg Anesthesiol. 2016;26(3):198–204.
5. Pritchard C, Radcliffe J. General principles of postoperative neurosurgical care. Anaesth Intens Care Med. 2008;9(6):231–6.
6. Berlowitz DJ, Wadsworth B, Ross J. Respiratory problems and management in people with spinal cord injury. Breathe (Sheff). 2016;12(4):328–40.
7. Stieglitz S. Noninvasive ventilation in cord paralysis diseases: is it a possible safe indication? In: Esquinas A, editor. Noninvasive mechanical ventilation. Cham: Springer; 2016. p. 445–50. https://doi.org/10.1007/978-3-319-21653-9_54.
8. Carrillo A, Lopez A, Bayoumy P. Noninvasive ventilation in acute respiratory failure and severe neurological deterioration. In: Esquinas A, editor. Noninvasive mechanical ventilation. Cham: Springer; 2016. p. 435–44. https://doi.org/10.1007/978-3-319-21653-9_53.
9. Boone MD, Jinadasa SP, Mueller A, et al. The effect of positive end-expiratory pressure on intracranial pressure and cerebral hemodynamics. Neurocrit Care. 2017;26:174–81.
10. Esquinas AM, Jover JL, Úbeda A, et al. Non-invasive mechanical ventilation in the pre- and intraoperative period and difficult airway. Rev Esp Anestesiol Reanim. 2015;62(9):502–11.
11. Ambrosino N, Guarracino F. Unusual applications of noninvasive ventilation. Eur Respir J. 2011;38:440–9.
12. Sy H. Noninvasive ventilation in neurocritical care. In: Esquinas AM, et al., editors. Noninvasive ventilation in sleep medicine and pulmonary critical care. Cham: Springer; 2020. p. 361–8. https://doi.org/10.1007/978-3-030-42998-0_37.
13. Lima WA, Campelo AR, Gomes RL, et al. The impact of positive end-expiratory pressure on cerebral perfusion pressure in adult patients with hemorrhagic stroke. Rev Bras Ter Intensiva. 2011;23(3):291–6.
14. Sah HK, Akcil EF, Tunali Y, et al. Efficacy of continuous positive airway pressure and incentive spirometry on respiratory functions during the postoperative period following supratentorial craniotomy: a prospective randomized controlled study. J Clin Anesth. 2017;42:31–5.

27

Assessment of Right Ventricular Function in Pulmonary Hypertension

Dorina Esendagli and Gulseren Elay

Abstract

Pulmonary hypertension (PH) can affect the course of different lung diseases, mainly chronic obstructive lung disease (COPD), interstitial lung diseases (ILD), and obesity hypoventilation syndrome (OHS). It is crucial to diagnose PH by using biomarkers, pulmonary function testing, imaging modalities, echocardiography, and, if possible, the gold standard test right heart catheterization. Noninvasive ventilation can improve PH-related symptoms in these patients.

Keywords

Pulmonary hypertension · Noninvasive ventilation · Chronic obstructive lung disease Interstitial lung diseases · Obesity hypoventilation syndrome

Abbreviations

6MWD	6-min walk distance
COPD	Chronic obstructive lung disease
DLCO	Diffusing capacity of the lung for carbon monoxide
FEV1	Forced expiratory volume
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
ILD	Interstitial lung diseases
IPF	Idiopathic pulmonary fibrosis
LA	Left atrium
mPAP	Mean pulmonary arterial pressure
NIV	Noninvasive mechanical ventilation
OHS	Obesity hypoventilation syndrome
OSAS	Obstructive sleep apnea syndrome
$PaCO_2$	Partial pressure of carbon dioxide
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RA	Right atrium
RV	Right ventricular
SvO_2	Mixed venous oxygen saturation
WU	Wood units

D. Esendagli (✉)
Department of Chest Diseases, Baskent University, Ankara, Turkey

G. Elay
Department of Internal Medicine, Intensive Care Unit, Gaziantep University, Gaziantep, Turkey

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_27

27.1 Introduction

Pulmonary hypertension (PH) can be encountered in many different diseases and its presence can affect both the prognosis and the survival of patients. Early diagnosis and appropriate treatment according to the underlying pathology are crucial for a better outcome. In this chapter we will focus mainly on the role right ventricular function and PH have in chronic lung diseases and the benefit noninvasive ventilation has in certain conditions. PH presence may not correlate with other pulmonary function tests and points out a specific group of patients who have a certain genetic signature usually with a worse outcome. Patients who are progressing and have a bad prognosis even with the maximum available treatment should undergo extensive diagnostic testing to confirm PH and identify the underlying cause to begin the appropriate treatment.

27.2 Discussion and Analysis of the Main Topic

27.2.1 Definition and Clinical Classification of PH

Symptoms and signs of PH are not specific, and its diagnosis is often delayed as clinicians are mainly focused on treating the underlying disease and suspect PH only when the medical condition becomes worse or progressing. Typically patients present with dyspnea and fatigue that progress over time, and years later severe pulmonary hypertension and right ventricular failure can develop. Chest pain especially when exercising, edema, abdominal pain, and swelling are some other common symptoms [1]. A detailed physical examination is crucial for differential diagnosis. Increased intensity of the pulmonic component of the second heart sound, signs of right ventricular failure, elevated jugular venous pressure, wide splitting of the second heart sound, a holosystolic murmur of tricuspid regurgitation, hepatomegaly, a pulsatile or tender liver, peripheral edema, ascites, and pleural effusion are the most common physical signs [1].

Table 27.1 Clinical classification of pulmonary hypertension

PAH
PH due to left heart disease
PH due to lung disease and/or hypoxia
PH due to pulmonary artery obstructions
PH with unclear and/or multifactorial mechanisms

PH pulmonary hypertension, *PAH* pulmonary arterial hypertension

Based on etiology and the underlying cause, patients with PH are classified mainly into five groups (Table 27.1).

Patients in group 1 are considered to have pulmonary arterial hypertension (PAH), which has several causes like inheritable diseases, various drugs, and connective tissue disorders. Whereas patients in group 2 are mainly the ones who develop PH because of a cardiac pathology usually due to left-sided heart diseases. Group 3 that includes the PH due to chronic lung disorders and hypoxemia will be the main group discussed in detail in this chapter. Group 4 includes mainly pulmonary artery obstructions and chronic thromboembolic PH, and group 5 is the group of PH as a result of unclear or multifactorial mechanisms [2].

Another classification for PH is pre- or post-capillary PH presence. In pre-capillary PH the primary elevation of pressure is in the pulmonary arterial system whereas in post-capillary PH the elevation of pressure is in the pulmonary venous and pulmonary capillary systems. Group 3 that includes lung diseases is mainly defined as being a pre-capillary one with a pulmonary arterial wedge pressure less than 15 mmHg and a pulmonary vascular resistance greater than 3 Wood units [2]. Some patients might have mixed pre-and post-capillary features (Table 27.2).

27.3 PH in Chronic Lung Disease and Hypoxia

PH is present in a subset of patients with chronic lung disease, and it usually has been shown to be related to bad prognosis and poor outcome. The etiology behind PH development in only a frac-

Table 27.2 Pre- and post-capillary pulmonary hypertension

Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR ≥3 WU
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR <3 WU
Combined pre-and post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ≥3 WU

PH pulmonary hypertension, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *WU* wood units

tion of patients is still not clearly understood, and the degree of pulmonary artery pressure sometimes can be very high and cannot be justified with only the underlying lung disease. The detection of PH in suspected patients can be performed initially by noninvasive methods. The plasma levels of N-terminal pro-BNP are usually elevated in severe PH patients but the specificity is low since it can be influenced by other heart diseases. Pulmonary function tests that are routinely performed for the diagnosis of lung disease and follow-up of patients can also be used for PH diagnosis, and usually diffusing capacity of the lung for carbon monoxide (DLCO) and exercise capacity are decreased together with impaired gas exchange even at rest. Imaging modalities that can help to calculate a ratio greater than 1 of the pulmonary artery to ascending aorta can be used as a tool for PH detection in IPF and COPD patients. On the other hand, the gold standard technique for PH is right heart catheterization that should be performed in patients with clinical progression and worsening gas exchange abnormalities or exercise limitations. The suggested diagnostic measurements for mild to moderate PH in lung diseases are mPAP 21–24 mmHg with PVR ≥3 WU, or mPAP 25–34 mmHg. Severe PH is defined as mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg with a low cardiac index. Sometimes it can be difficult to decide if a patient belongs to group 1 or group 3 for PH, and the criteria favoring group 3 are mainly the following: FEV1˂% predicted value for COPD, FVC ˂ 70% predicted value for IPF, a compatible DLCO result with the changes in spirometry, reduced breathing reserve, mixed venous oxygen saturation above lower limit, increase in $PaCO_2$ during exercise, typical airway and parenchymal changes shown on high resolution computed tomography of the chest (HRCT), and PH of mild to moderate degree [3]. There is a lack of data on this field as few randomized controlled trials have been performed, and we will focus mainly on the lung diseases that have been studied so far.

27.3.1 COPD

PH prevalence in COPD depends on both the severity of the disease and the method used to diagnose it. Some studies have even shown that in a subgroup of COPD patients there does exist a genetic signature that predisposes to PH development. A majority of severe COPD patients who are classified as GOLD stage 4 have a mPAP greater than 20 mmHg. Of these, 1–5% of patients are classified as severe PH. A pulmonary vascular COPD phenotype has been defined for patients who have a severe decrease in airflow and DLCO, normo- or hypocapnia, and cardiovascular exercise limitation. Studies have shown that radiology for mild to moderate and severe PH-COPD patients is not different and that usage of echocardiography had only a weak correlation with systolic PAP measured by right heart catheterization. These findings suggest that COPD patients who are progressing or have a bad prognosis should be further evaluated with invasive methods like right heart catheterization as they cannot be identified by noninvasive measurements like echocardiography or imaging techniques; thus under evaluation is a matter of concern. Hurdman et al. have identified predictors of survival in COPD patients with pulmonary hypertension that consist of age, DLCO, mixed venous oxygen saturation (SvO_2), and WHO functional class. A SvO_2 less than 65% and DLCO less than 27% could be used to define the subgroup with a worse outcome within PH-COPD patients. This group of patients was shown to be more hypoxemic and hypocarbic instead of hypercarbic due to hyperventilation. Interestingly the correction of hypoxia by providing supportive oxygen treat-

ment did not lead to an improvement of PAP, and this supports the idea that hypoxia is not the only cause driving PH in COPD patients. COPD is a disease that can present with exacerbations, and since the measurement of PAP might not reflect the real value in presence of an attack it is recommended that PH assessment be performed when the patients are in stable disease [4].

Meta-analysis regarding PAH-targeted therapies in PH-COPD patients has shown a benefit in hemodynamic effects with sildenafil and bosentan. On the other hand, no distinct improvement could be shown in the 6-min walk distance (6MWD) test, dyspnea, and quality of life; thus, further and larger studies are needed in this field to define a possible benefit of these medical drugs in COPD patients.

27.3.2 ILD

Interstitial lung diseases have also been associated with PH development in a portion of patients, but current knowledge is mostly about idiopathic pulmonary fibrosis (IPF). A correlation of IPF severity and the frequency of the presence of PH has been shown. Even at the initial screening of newly diagnosed IPF patients, 8–15% have a mPAP greater than 25 mmHg. In advanced IPF, PH frequency is around 30–50% and in end-stage disease it is more than 60%, thus stressing the importance of right heart assessment in this group of patients. The presence of PH harms the prognosis and survival of IPF patients and like COPD there is poor correlation with lung function impairment and HRCT findings. Some studies have shown a genetic predisposition for some IPF patients to develop PH and to progress rapidly, which is also related to a poorer prognosis when compared to other causes of PH [3].

Another group of patients is those with combined pulmonary fibrosis and emphysema with a prevalence of PH as high as 30–50%. Patients have a significant decrease in DLCO, and deep hypoxemia and survival rates are low. Clinical trials regarding PH treatment with PAH-specific drugs in these groups of patients have shown that riociguat and ambrisentan are contraindicated and that other drugs, despite an average improvement of 46 m in the 6MWD, were of no benefit in dyspnea or improving quality of life, suggesting that the usage of these drugs should be studied further in detail.

27.3.3 OHS

Obesity is a matter of concern because of increased incidence and its relation to high morbidity and mortality. Obesity is related to both obesity hypoventilation syndrome (OHS) and obstructive sleep apnea-hypopnea syndrome (OSAS). Alveolar hypoventilation is shown to be the most important driving factor for PH development in this group of patients. It is an interesting fact that the presence of hypoxia or hypercapnia is not enough for the pathogenesis since not all these patients have PH, and administration of oxygen did not reduce PAP value or improved hemodynamics in OHS patients. Studies have shown that OSAS alone can increase PAP above the normal limit. The prevalence of right ventricular overload is quite frequent in OHS patients ranging from 43.3% to 58% depending on the cut-off value for PAP, and the technique used for the diagnosis is either an invasive one like right heart catheterization or a noninvasive method like echocardiography. Since the latter is difficult to perform in obese patients the usage of noninvasive methods as a diagnostic tool can underestimate the presence and severity of PH in this group of patients.

27.3.4 Other Diseases

Sarcoidosis has also a high incidence of PH ranging from 5.7 to 74%. The presence of PH in this group of patients is usually shown in diffuse parenchymal involvement and is related to poor survival. The etiology for PH is multifactorial including remodeling and fibrosis, compression by lymphadenopathies of pulmonary vessels, left ventricular dysfunction, and portopulmonary hypertension.

PH can be present in Langerhans cell histiocytosis, lymphangioleiomyomatosis, chronic hypersensitivity pneumonitis, bronchopulmonary dysplasia, cystic fibrosis, and even lung cancer patients.

There are still not enough data for the approval of PAH-targeted drugs in the treatment of PH in this group of diseases.

27.4 PH and Noninvasive Ventilation

The presence of PH in lung diseases is a sign of bad prognosis and poor outcome, and not enough data are present regarding the usage of certain medications in these groups of patients. Regarding the usage of noninvasive ventilation as a means of treatment in both COPD and OHS patients that develop hypercapnia, a few studies have been performed to investigate its role in PH as well.

27.4.1 COPD Including Exacerbations

There are only a few studies regarding the benefit of NIV in COPD patients who are diagnosed with PH. Long-term NIV usage was shown to improve gas exchange but not pulmonary function in COPD patients [5]. The mPAP value did not change after NIV for COPD but it was reduced for patients who had thoracic restriction. One of the reasons for the lack of response to NIV might be mechanical distortion that is caused by progressive airway obstruction and which is not expected to be changed. Another study investigated the role of NIV in PH-COPD patients with acute exacerbations and showed an improvement of blood gas parameters, walking autonomy, and symptoms for patients with a systolic pulmonary artery pressure less than 55 mmHg. Unfortunately, COPD patients with severe PH had a poor response to NIV treatment [6].

27.4.2 OHS

Different studies have been performed regarding the effect of NIV on OHS patients including different periods of time starting from 3 months to 12 years follow-up. Held et al. showed that with only 3 months of treatment with NIV systolic, diastolic, mPAP together with PVR decreased, and improvement up to 66 m was observed in the 6MWD test [7]. The volume of the right atrium (RA) decreased, left atrium (LA) increased, and right ventricular (RV) function improved. Cardiac function improvement was also accompanied by decreased serum NT-proBNP levels. Another study showed a decrease in mean systolic PAP in patients with right ventricular overload and a significant increase in the 6MWD test after 6 months of NIV treatment. A longitudinal, observational study that included OHS patients in a home ventilation program for 12 years showed that bi-level positive airway pressure led to improvement of FEV1 and FVC and blood gas values. In this study, FVC was shown as the predictor factor for mortality for this group of patients [8, 9].

27.5 Conclusion Discussion

The assessment of right ventricular function and the presence of PH in patients with lung diseases are important in order to estimate prognosis and outcome. Unfortunately there are not enough data regarding the treatment of PH in this group of patients, and further studies are crucial in the field. Development of animal models, research on novel biomarkers, and clinical trials are encouraged. Future studies that focus on identification of patients at risk and aim at the prevention or reversal of vascular remodeling are important. The role of specific drugs in prognosis/survival and the usage of NIV for subgroups of patients that might benefit are matters of concern that should be enlightened.

Key Major Recommendations

- The presence of PH and right ventricular assessment are recommended for progressing chronic lung diseases with worse outcomes.
- NIV treatment has been shown to reduce mPAP in OHS but not in COPD patients.
- PAH-targeted therapies in group 3 PH patients need further investigation.

References

1. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J. 2019;53.
2. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913.
3. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53(1):1801914.
4. Hurdman J, Condliffe R, Elliot CA, Swift A, Rajaram S, Davies C, Hill C, Hamilton N, Armstrong IJ, Billings C, Pollard L. Pulmonary hypertension in COPD: results from the ASPIRE registry. Eur Respir J. 2013;41(6):1292–301.
5. Schönhofer B, Barchfeld T, Wenzel M, Köhler D. Long term effects of non-invasive mechanical ventilation on pulmonary haemodynamics in patients with chronic respiratory failure. Thorax. 2001;56(7):524–8.
6. Parola D, Romani S, Petroianni A, Locorriere L, Terzano C. Treatment of acute exacerbations with non-invasive ventilation in chronic hypercapnic COPD patients with pulmonary hypertension. Eur Rev Med Pharmacol Sci. 2012;16(2):183–91.
7. Held M, Walthelm J, Baron S, Roth C, Jany B. Functional impact of pulmonary hypertension due to hypoventilation and changes under noninvasive ventilation. Eur Respir J. 2014;43(1):156–65.
8. Castillejo EO, de Lucas RP, Martin SL, Barrios PR, Rodríguez PR, Caicedo LM, Cano JM, Gonzalez-Moro JM. Noninvasive mechanical ventilation in patients with obesity hypoventilation syndrome. Long-term outcome and prognostic factors. Arch Bronconeumol (English Edition). 2015;51(2):61–8.
9. Castro-Añón OL, Golpe R, Pérez-De-Llano LA, Lopez Gonzalez MJ, Escalona Velasquez EJ, Perez Fernandez R, Testa Fernandez A, Gonzalez Quintela A. Haemodynamic effects of non-invasive ventilation in patients with obesity-hypoventilation syndrome. Respirology. 2012;17(8):1269–74.

Part IV

Lung Function Measurement in Noninvasive Ventilation Are There Any Impact of Implementation?

28 Equipment for Pulmonary Function Evaluation: Devices and Technology

Márcia Araújo, Sara Dias, Bruno Cabrita, and Bárbara Seabra

Abstract

Pulmonary function tests are essential for the diagnosis and management of pulmonary diseases. Spirometry is the most commonly used test and can be complemented by body plethysmography that is capable of measuring all lung volumes and airway resistance. Another important test is the diffusing capacity for carbon monoxide that indirectly evaluates the alveolar-capillary interface. Impulse oscillometry may add useful information to the remaining lung function tests. The equipment and technology used in these tests will be discussed in this chapter.

Keywords

Pulmonary function test · Equipment · Spirometry · Plethysmography · Diffusing capacity of carbon monoxide

Abbreviations

ATS	American Thoracic Society
CO	Carbon monoxide
DLCO	Diffusing capacity for carbon monoxide
ERS	European Respiratory Society
FACQ	Alveolar carbon monoxide fraction
FEV1	Forced expiratory volume in one second
FOT	Forced oscillation technique
FRC	Functional residual capacity
FVC	Forced vital capacity
IOS	Impulse oscillometry system
ISO	International Organization for Standardization
PaCO	Partial pressure of carbon monoxide
Raw	Airway resistance
RGAs	Rapid gas analyzers
RV	Residual volume
sRaw	Specific airway resistance
TLC	Total lung capacity
Va	Alveolar volume

28.1 Introduction

Pulmonary function tests are essential for the diagnosis and the management of pulmonary diseases.

Spirometry is the most commonly used pulmonary function test that is particularly useful

M. Araújo (✉) · S. Dias · B. Cabrita · B. Seabra
Pulmonology Department at Hospital Pedro Hispano, Matosinhos, Portugal
e-mail: Barbara.Seabra@ulsm.min-saude.pt

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_28

due to its accessibility and relative simplicity [1, 2]. Its most relevant measurements are forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC ratio [2].

There are two major types of spirometers: volume displacement spirometers (wet and dry spirometers) and flow-integrated pneumotachographs. Continuous improvement in spirometry hardware and software led to the development of numerous types of spirometers from the large apparatus used in laboratories to portable ones used for telemonitoring [1, 3–5].

Body plethysmography is capable of measuring static lung volumes such as functional residual capacity (FRC), total lung capacity (TLC), and airway resistance (Raw) [6]. There are three types of plethysmographs: variable-pressure plethysmograph, volume-displacement, and, most recently, pressure-corrected variable-volume plethysmograph [7]. The apparatus consists of a sealed glassed box similar to a telephone box. The flow rates are measured by a spirometer and pressure changes inside the box and the patient's mouth are measured by a transducer [6].

The *diffusing capacity for carbon monoxide (DLCO)* evaluates the alveolar-capillary interface, and its structural and functional properties. Classically, gas analyzers used a sample of the exhaled gas to determine DLCO. These are progressively being replaced by modern rapid gas analyzers (RGAs) capable of continuous measurement of DLCO. Despite the evolution of the devices over time all the equipment relies on the same basic principles [8].

Oscillometry is used to measure mechanical properties of the respiratory system during tidal breathing. It can be used as an alternative to traditional lung tests in patients who are unable to perform "traditional" lung function maneuvers, such as small children and mechanically ventilated patients. The impulse oscillometry system (IOS) has a loudspeaker that generates an oscillating pressure into the respiratory tract and uses the breathing activity response to assess lung function [7, 9].

28.2 Discussion and Analysis of the Main Topic

28.2.1 Spirometry

Spirometry is an essential tool in respiratory medicine. Besides diagnosing lung disease and monitoring lung function, especially obstructive airway disorders, it is also useful for assessing prognosis and preoperative risk in some patients [1, 2]. Despite its utility and accessibility, spirometry has a major downside: its dependency on patient cooperation [2].

There are two major types of spirometers: volume displacement spirometers (e.g., wet and dry spirometers) and flow-integrated pneumotachographs [1, 10].

Volume-measurement spirometers, as their name implies, measure volume and calculate flow [11]. These spirometers have the advantage of being highly accurate. However, they are large, have several moving parts, and are expensive [1, 10, 11]. This equipment can be divided into wet and dry spirometers [11].

Flow-measurement spirometers measure flow directly while volume is calculated indirectly. It is the most common technology used in labs. Fleish and Lilly types of pneumotachographs were used in the past. Nowadays pneumotachographs use the pressure difference generated by the flow passing through a resistance, normally a sieve resistance [10, 11]. Typically these are small and portable devices without moving parts. As for disadvantages, this system needs more frequent calibration when compared to the volume-measurement spirometer and can be contaminated with sputum or moisture [1, 10].

There are other less common types of spirometers. One type consisted of a *turbine flow meter* (Fig. 28.1), which determined the flow passing through the device based on the speed of the rotating vane inside the device [10]. One of its drawbacks was that with high flows the vane could continue rotating after the flow had stopped [11]. However, nowadays, we have turbine spirometers of high reliability and with little necessity of calibration [10].

Fig. 28.1 Turbine flow meter spirometer

Another option is the *mass flow sensor (anemometer)*. The flow is determined based on a temperature decrease caused by the gas flow passing through a wire electrically heated to a constant temperature [10, 11]. However, the sensor resistance is connected with cables and connectors, and changes in those components can interfere with the airflow measurement [11].

Finally, we have *ultrasonic spirometers*. The flow passing through the device accelerates ultrasound waves flowing in the same direction but slows down the waves flowing in the opposite direction. The time difference between waves is used to measure flow [10]. This type of technology is generally expensive [11].

All spirometers must meet the standards according to the current update of the International Organization for Standardization (ISO) 26782 [2]. In 2019 the ATS and ERS issued an update of the technical statement for the standardization of spirometry.

With the advances in technology we dispose of numerous types of spirometers from the larger ones used in labs to portable ones. The *office spirometers* are characterized by their small size and lower cost. However, they have low precision in FVC measurement and inability to show volume-time or flow-volume curves, although it appears that in patients already diagnosed with an obstructive lung disease the values of FEV1 e FVC correlate with the ones measured by laboratory spirometry [4, 5].

Pocket spirometers are small, portable, and of low cost. They are used for measuring FEV1 e FEV6 and monitoring patients at home [5]. In this field, recent technological advances have developed smartphone apps capable of obtaining real-time spirometry results from a spirometer connected by Bluetooth to the smartphone. These systems can be used for self-management of the disease in asthmatic patients, for example [3].

28.2.2 Whole-Body Plethysmography

Body plethysmography allows for the measurement of static pulmonary volumes such as the residual volume (RV), total lung capacity (TLC), and functional residual capacity (FRC) as well as assessing airway resistance: sRaw and Raw. Despite being the gold standard in lung function, spirometry cannot measure all lung volumes; therefore, plethysmography is an important and complementary study providing a more detailed analysis [6].

The apparatus consists of a glass sealed chamber with 700–1000 L of volume, where the subject sits, with a controlled leak to stabilize the internal pressure. It has a pressure transducer to measure the pressure inside the plethysmograph and another one to measure the pressure inside the patient's mouth. The respiratory flow is measured by conventional equipment already described above in the spirometry equipment [6, 7].

This system's technology is based upon the law of Boyle-Mariotte that correlates pressure and volume changes [6, 7]. Using changes in the box pressure, mouth pressure, and flow rate we can determine static lung volumes and airflow resistance [6]. Usually, sRaw is the first parameter to be measured, then FRC, and, lastly, the remaining lung volumes by spirometry methods [7]. Raw can be interpreted as a measure of airway obstruction and corresponds to the ratio of sRaw to FRC [6]. One important concept used to

determine sRaw and FRC is the shift volume. To initiate an inspiration or expiration it is necessary to create a pressure gradient. At inspiration, for example, the contraction movements of the respiratory muscles cause an increase in lung volume, and, therefore, a decrease in alveolar pressure occurs leading to airflow into the lungs. This volume change, needed to provide a gradient for inspiratory/expiratory flows, is named shift volume [6, 7]. This parameter is assessed during a shutter maneuver, and it is deducted from volume/pressure changes caused in the plethysmograph sealed box with decompression and compression movements [6]. The shutter maneuver consists of transient airway obstruction while the patient makes respiratory efforts and changes in mouth pressure are measured; in this condition mouth pressures are considered equal to alveolar pressure [6, 7].

Whole-body plethysmography has been improving since the first equipment, the *constant-volume or variable-pressure plethysmograph* [6]. It was used to measure small volume changes occurring during compression and decompression of thoracic gas while the patient breathed entirely within the plethysmograph. To detect such minor pressure changes a very sensitive pressure transducer was necessary. Despite its simplicity this plethysmograph had good accuracy [7].

The *constant-pressure or volume-displacement plethysmograph* was used to measure large volumes, assessing volume changes of the thorax directly. In contrast to the previous model, in this type of plethysmograph the patient breathed in and out across the wall of the plethysmograph. When compared to the constant volume plethysmograph, it had the advantage of measuring slow or forced vital capacity but given the difficulty in building this type of machine and the recent technology improvements it has been supplanted by the flow plethysmograph [7].

The *pressure-corrected variable-volume plethysmograph* (Fig. 28.2), also known as a transmural plethysmograph or flow plethysmograph, is a combination of the two systems presented above: it is capable of measuring pressure and volume changes with high sensitivity. The low sensitivity for small volume changes typical of the volume-displacement plethysmograph, in this equipment, can be compensated with the occlusion of the pneumotachograph that converts the machine into a variable-pressure plethysmograph. Thereby with the same equipment it is possible to obtain sensitive measurements of maximal expiratory flow-volume curves, FRC, sRaw, and Raw, allowing to distinguish thoracic gas compression and airway trapping. Beyond that, it is less dependent on patient cooperation when compared to the previous models [7]. The last ATS/ERS update concerning the standardization of measurement of lung volumes using body plethysmography was in 2005 [12].

Fig. 28.2 Plethysmograph

28.2.3 Diffusing Capacity for Carbon Monoxide

The exchange between O_2 and CO_2 is the main function of the lungs, depending on ventilation, alveolo-capillary diffusion, and perfusion [7]. There are many types of equipment capable of measuring DLCO, although the basic principles are the same. The determination of DLCO is based upon equations using alveolar volume (Va), alveolar carbon monoxide fraction (FACQ), and partial pressure of carbon monoxide (PaCO). In patients with decreased DLCO it is possible to determine the components of the DLCO and differentiate the causes: interstitial/capillary pathology [8].

The system uses a tracer gas that must be inert, has a diffusion capacity identical to carbon monoxide, and is absent from alveolar gas or has a known concentration. The most commonly used tracer gases are helium (He) and methane, which are important to determine the alveolar volume and alveolar concentration of carbon monoxide [8]. The flows can be measured with flow integrated pneumotachographs [7].

In classical DLCO systems the patient breathes through a two-way valve system and after a maximal expiration the subject inhales a gas mixture with carbon monoxide (CO) and a tracer gas from a container. Then 1500 mL volume of exhaled air is required; the first 750 mL is used for washout of airways and device dead space and the other 750 mL is analyzed [7]. This maneuver, named *single-breath method*, involves a breath-holding period of 10 s at TLC before exhaling [7, 8]. Although for patients with obstructive disease, without sufficient flows to perform rapid inspiration or expiration, the three equations method can increase the accuracy of the test [7].

Nowadays the most commonly used system is the rapid gas analyzer (RGA), which is capable of real-time measuring carbon monoxide during a single and slow exhalation with a constant flow, after a breath-holding period of only 1–2 s [7, 8]. In this case, the patient does not need to exhale 1500 mL volume of air and only needs a brief period of breath-holding; however, not every patient will be able to perform a low and constant flow exhalation. Due to the continuous measurement of DLCO, RGAs can be useful for the identification of unequal distributions of transfer factor or ventilation [7]. ERS and ATS last updated in 2017 the technical standards for single-breath carbon monoxide especially in relation to RGAs [8].

In children or very ill patients a multiple breath method can be used: the steady-state method or the rebreathing method. In the steady-state method, the patient breathes from a gas container for a certain period of time. In the rebreathing method the patient had to hyperventilate with a large tidal volume for about 30 s from a closed system with a gas mixture containing CO and He. Nowadays we have rebreathing methods at normal resting ventilation [7].

There are some extrinsic factors capable of influencing DLCO measurements that must be taken into the account. One of them is hemoglobin concentration, which always requires correction. In patients administered supplementary O_2 the oxygen supply must be disconnected for at least 10 min before the test, and for smokers the CO back tension requires correction. Another important aspect is body position; for the measurement of DLCO the patient must be seated upright because of the uneven physiological distribution of blood flow in the lungs in this position [7]. Furthermore, because of the recruitment of the upper lung zone with physical activity, patients must rest for 5 min before starting the test and between maneuvers an interval of 4 min of rest and seated is required, although patients with airflow obstruction may require a longer period [7, 8].

28.2.4 Oscillometry

Oscillometry measures the mechanical properties of the respiratory system during tidal breathing assessing obstruction in the large and small peripheral airways as well as bronchodilator response and bronchoprovocation testing [9]. Since it requires minimal patient cooperation, it is suitable for use in both children and adults and

may be used in subjects who are unable to perform a spirometry or a plethysmography test, including mechanically ventilated patients [7, 9]. From home monitoring to intensive care units it has a wide range of clinical application settings [9].

The equipment applies an oscillating pressure signal into the respiratory tract and uses pressure or flow responses to determine input impedance (resistance and reactance) that represents the total mechanical properties of the respiratory system [9]. ERS last updated the technical standards for respiratory oscillometry in 2020 [9].

The first equipment available, the *forced oscillation technique (FOT)*, used a single frequency wave [13]. Nowadays, the *impulse oscillometry system (IOS)* uses multiple wave frequencies and may be more sensitive to detect small airway obstruction when compared to spirometry [9, 13].

The IOS apparatus has a loudspeaker that generates pressure impulses with a frequency range of 4–50 Hz. The lower frequencies are capable of reaching small airways while high frequencies are used to assess large airways. Frequencies below 4 Hz may be generated by a piston-type mechanical device, pneumatic proportional solenoid valves, or a loudspeaker [9, 13]. Conversely, frequencies above 35 Hz can be produced by woofer speakers or by an interrupter valve, which is seldom used [9]. The loudspeaker is connected by a y-adaptor to a terminal resistor that provides a low-impedance pathway. The resulting impulse pressure is then transmitted to the respiratory tract through the pneumotachograph and mouthpiece. A pneumotachograph and an attached pressure transducer receive the breathing activity information, and the flow and pressure signals are then processed by an analog-to-digital converter [7].

28.3 Conclusion Discussion

Spirometry is the most commonly used pulmonary function test [1]. The spirometers can be divided into two major types: volume-measurement and flow-measurement spirometers which are the most commonly used in labs. Many advances have been made since the first spirometers. Nowadays we have numerous types of technology from small and simple portable devices to sophisticated and expensive ones [11].

Whole-body plethysmography is the gold standard for measuring lung volumes; it measures static lung volumes and airway resistance. Initially, there was a variable-pressure plethysmograph used to measure small volume changes, then volume-displacement for large volumes, and, finally, the pressure-corrected variable-volume plethysmograph that combines the technology found in the two previous models [7].

DLCO evaluates the alveolar-capillary interface. Previously with simple gas analyzers a sample of exhaled gas was collected and then analyzed; nowadays with RGAs a continuous measurement of DLCO during an entire maneuver is possible. The most common methodology used to measure DLCO is the single-breath technique that implies measuring the uptake of carbon monoxide from the lung after a breath-holding period [8].

The impulse oscillometry system (IOS) uses multiple wave frequency impulses to assess lung function through the measurement of both airway resistance and airway reactance [13]. It may be used in children and adults but is particularly useful for evaluating patients unable to perform traditional lung function measurements [9].

The lung function tests are an essential tool in respiratory medicine. There has been a lot of improvement in this field in the past years, allowing the emergence of more accurate and sophisticated equipment. For each of these devices and tests there are ERS and ATS standardization recommendations.

Key Major Recommendations

- Pulmonary function tests are essential for the diagnosis and management of pulmonary diseases.
- There are two major types of spirometers: volume displacement spirometers and flow-integrated pneumotachographs.
- Body plethysmography allows for the measuring of static pulmonary volumes and airway

resistance. The most commonly used system is the pressure-corrected variable-volume plethysmograph.

- DLCO evaluates the alveolar-capillary interface and with systems nowadays, RGAs, it is possible to measure DLCO continuously during a maneuver.
- Oscillometry measures the mechanical properties of the respiratory system and is useful in patients unable to perform traditional lung function tests.

References

1. Liou TG, Kanner RE. Spirometry. Clin Rev Allergy Immunol. 2009;37(3):137–52. https://doi.org/10.1007/s12016-009-8128-z.
2. Graham BL, Steenbruggen I, Barjaktarevic IZ, et al. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200(8):E70–88. https://doi.org/10.1164/rccm.201908-1590ST.
3. Ljungberg H, Carleborg A, Gerber H, et al. Clinical effect on uncontrolled asthma using a novel digital automated self-management solution: A physician-blinded randomised controlled crossover trial. Eur Respir J. 2019;54(5):1–11. https://doi.org/10.1183/13993003.00983-2019.
4. Tupper OD, Gregersen TL, Ringbaek T, et al. Effect of tele–health care on quality of life in patients with severe COPD: A randomized clinical trial. Int J COPD. 2018;13:2657–62. https://doi.org/10.2147/COPD.S164121.
5. Lopes AJ. Advances in spirometry testing for lung function analysis. Expert Rev Respir Med. 2019;13(6):559–69. https://doi.org/10.1080/17476348.2019.1607301.
6. Criée CP, Sorichter S, Smith HJ, et al. Body plethysmography: its principles and clinical use. Respir Med. 2011;105(7):959–71. https://doi.org/10.1016/j.rmed.2011.02.006.
7. Hainsworth R. Lung function testing. In: European respiratory monographs, vol. 10; 2006. p. 605–13. https://doi.org/10.1016/B978-0-323-03707-5.50056-5.
8. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017;49(1):1–31. https://doi.org/10.1183/13993003.00016-2016.
9. King GG, Bates J, Berger KI, et al. Technical standards for respiratory oscillometry. Eur Respir J. 2020;55(2):1–21. https://doi.org/10.1183/13993003.00753-2019.
10. Garcia-Rio F, Calle M, Burgos F, et al. Espirometria. Arch Bronconeumol. 2013;49(9):388–401. https://doi.org/10.1016/j.arbres.2013.04.001.
11. de Jongh F. Spirometers. Breath. 2018;4(3):45–52. https://doi.org/10.4324/9781315110653-5.
12. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511–22. https://doi.org/10.1183/09031936.05.00035005.
13. Brashier B, Salvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulse oscillometry system. Breathe. 2015;11(1):57–65. https://doi.org/10.1183/20734735.020514.

Oxygen Supplementation: High-Flow Nasal Oxygen

29

Mohamad F. El-Khatib

Abstract

High-flow nasal cannula (HFNC) oxygen supplementation has several physiological advantages compared with other standard oxygen therapies, including washing out anatomical dead space, generation of positive airway pressure, providing constant oxygen concentrations, and optimal heating and humidification of delivered gas. HFNC has emerged as an effective modality for early treatment of adults with respiratory failure with diverse underlying diseases. This chapter covers the mechanisms of HFNC and its potential use in common clinical settings.

Keywords

High-flow nasal cannula · Oxygen supplementation · Conventional oxygen therapy · Mechanisms · Clinical use

Abbreviations

AHRF	Acute hypoxemic respiratory failure
ARDS	Acute respiratory disease syndrome
CO_2	Carbon dioxide
COT	Conventional oxygen therapy
COVID-19	Coronavirus disease-19
CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
HFNC	High-flow nasal cannula
ICU	Intensive care unit
NIPPV	Noninvasive positive-pressure ventilation
O_2	Oxygen
PaO_2	Partial pressure of arterial oxygen
PEEP	Positive end expiratory pressure
SpO_2	Arterial oxygen saturation
WHO	World Health Organization

29.1 Introduction

Supplemental oxygen remains the first-line intervention in acute and chronic hypoxemic respiratory distress/failure. Fractions of inspired oxygen (FiO_2) at concentrations greater than room air (i.e., >21%) are usually delivered to hypoxemic

M. F. El-Khatib (✉)
Division of Respiratory Therapy, Department of Anesthesiology, American University of Beirut—Medical Center, Beirut, Lebanon
e-mail: mk05@aub.edu.lb

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_29

patients to reverse hypoxemia and alleviate respiratory distress symptoms and manifestations.

There are several medical devices for oxygen supplementation in patients with hypoxemic respiratory distress/failure [1]. These devices range from simple nasal cannulas to nonrebreathing masks. The choice of a specific device is based on several factors including the desired FiO_2 to be given to the patient, the range of oxygen flows allowed for the specific oxygen delivery device, and the patient's tolerance of the device.

The major challenge for clinicians at the bedside is to provide accurate and stable fractions of inspired oxygen at concentrations greater than room air and up to 100% that are required to alleviate hypoxemia. The traditional oxygen therapy devices including cannulas and masks (e.g., simple and nonrebreathing masks) are limited by their restricted flow rates (≤10 L/min), by suboptimal relative humidity ranges (50–80%), by poor tolerance, and, most importantly, by inaccurate and unpredictable levels of FiO_2s [1]. The oxygen flow rate requirements in patients with respiratory distress are usually high and often exceeds the oxygen flow rates provided through traditional oxygen delivery devices. As a result, patients will compensate for the needed flow rates and minute volume requirements by entraining room air. This will lead to dilution of delivered oxygen and subsequently compromise the capability of clinicians to deliver consistent and accurate FiO_2 for patients with hypoxemic respiratory distress [2].

29.2 Discussion and Analysis of the Main Topic

29.2.1 Mechanisms of Action of High-Flow Nasal Cannula

High-flow nasal cannula (HFNC) oxygen therapy is an alternative method for oxygen supplementation. HFNC devices allow modification of only two variables: the rate of gas flow and the percentage of oxygen being delivered. It generates extremely high flow rates (60–100 L/min) of air-oxygen mixture that is optimally humidified to 100% relative humidity and heated to 37 °C before delivering the mixture to the patient using a special nasal cannula interface (Fig. 29.1). The

Fig. 29.1 High-flow nasal cannula

air–oxygen mixture is achieved with an air-oxygen blender to allow the delivery of consistent and accurate FiO_2 in the range of 21–100%. HFNC has several physiological advantages and benefits over traditional oxygen therapy devices. It exerts a range of important and independent physiological effects on a variety of factors that may determine clinical outcomes for patients with acute respiratory failure (Table 29.1).

Since the air-oxygen mixture is optimally humidified and heated in HFNC systems, the balance of temperature and humidity that diminishes airway dryness and maintains the function of the mucociliary transport system is preserved for improved secretion clearance and minimal dependence on mucolytic agents. By delivering high gas flows directly into the nasopharynx, HFNC will induce flushing of carbon dioxide (CO_2) in the pharynx and create a reservoir of fresh gas that will minimize CO_2 rebreathing, reduce dead space, and increase the alveolar ventilation over minute ventilation ratio. Furthermore, the generated high flows that match or exceed the patients' peak inspiratory flow demands can decrease the nasopharyngeal resistance, thereby decreasing the resistive work of breathing. Some levels of positive airway pressure (2–6 cmH_2O) are generated during HFNC that induce a positive end inspiratory pressure (PEEP) effect in the lungs, which can prevent/minimize alveolar collapse and recruit atelectatic lung regions. The degree of generated PEEP effect is dependent on the flow rate, geometry of the patient's upper airway, breathing through the nose or mouth, and the appropriate size of the cannula relative to the patient's nares. During HFNC therapy, the accurate and consistent delivery of the required FiO_2 eliminates the need to switch among different oxygen therapy delivery systems as patients wean off oxygen requirements or their condition becomes more acute as HFNC can provide a wide range of stable FiO_2s (21–100%).

Table 29.1 Physiological benefits of high-flow nasal cannula oxygen therapy

Clinical features of HFNC	Physiological benefits
1. Optimal heating and humidification of inhaled air-oxygen mixture	– Improves mucociliary clearance
	– Decreases bronchoconstriction
	– Decreases metabolic cost of breathing
2. Washout of upper airways	– Decreases deadspace
3. High nasal inspiratory flow	– Decreases nasopharyngeal resistance
4. Continuous positive airway pressure	– Increases functional residual capacity
	– Increasing alveolar recruitment in the lungs
5. Limited entrainment of ambient air	– Stable and increased FiO_2

29.2.2 Application of HFNC in Clinical Settings

HFNC is simple and user friendly yet very versatile with beneficial outcomes in a wide range of diseases and medical conditions. In recent years, clinical uses of HFNC in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS), with coronavirus (COVID-19), with respiratory compromises induced by heart failure, by obstructive airway disease, and by respiratory infection, have emerged. Also, HFNC has been shown to be helpful as an adjunct in airway instrumentation, in the post-extubation period. Patients who are immunocompromised and with end-of-life management can benefit from the safety and simplicity of the technology while achieving desired end points. HFNC should not be restricted to critical care areas and can be used in a low-monitoring environment with no need for prior knowledge of techniques for invasive or noninvasive ventilatory support.

29.2.3 Acute Hypoxemic Respiratory Failure/ARDS

Among patients with acute hypoxemic respiratory failure (AHRF), HFNC therapy correlates with higher partial pressure of arterial oxygen,

lower respiratory rates, lower dyspnea scores, less mouth dryness, and is better tolerated and more comfortable than more traditional alternatives such as non-rebreathing or venturi oxygen masks. Short-term physiological effects of HFNC on inspiratory muscle effort and gas exchange and acid-base balance are positively more evident in comparison with conventional oxygen therapy in patients with AHRF [3]. These findings suggest that patients with AHRF can be safely managed with HFNC therapy particularly during the initial stages and that HFNC therapy can benefit a relatively good proportion of the total number of AHRF patients. In a multicenter, open-label trial, Frat et al. randomly assigned 310 patients without hypercapnia who had acute hypoxemic respiratory failure ($PaO_2/FiO_2 \leq 300$) to HFNC oxygen therapy, standard oxygen therapy delivered through a face mask, or noninvasive positive-pressure ventilation (NIPPV). Their outcomes were the proportion of patients intubated at day 28, all-cause mortality in the intensive care unit at 90 days, and the number of ventilator-free days at day 28. The intubation rate was 38% in HFNC oxygen group, 47% in the face mask group, and 50% in the noninvasive-ventilation group. Patients treated with HFNC oxygen therapy had more ventilator-free days (if intubated) and better survival rates [4]. Two recent meta-analyses compared HFNC oxygen therapy to conventional oxygen therapy (COT) and noninvasive ventilation in patients with acute hypoxemic respiratory failure [5, 6]. Mortality remains unaffected among the three therapies but HFNC oxygen therapy appears to be better tolerated than conventional oxygen therapy and noninvasive ventilation in these patients. Even though there seems to be an inclination to suggest that HFNC oxygen supplementation may reduce intubation rate, this issue remains controversial and more studies on the topic are needed.

HFNC therapy can be a useful treatment for ARDS due to COVID-19 either as a respiratory support alone or as a bridge therapy to orotracheal intubation. When administered in a unit monitored by an expert staff, HFNC therapy can avoid intubation in almost 50% of patients with COVID-19 or delay admission to an intensive care unit, without increasing overall mortality secondary to delayed intubation [7].

Optimal set flow rates during HFNC therapy remain elusive, heterogenous, and wide (15 L/min to 100 L/min) in published clinical studies despite that the set flow rate is the top parameter that influences HFNC success in patients with AHRF/ARDS, and the key question continues to be as to what is the best flow rate during HFNC treatment. In a prospective randomized crossover study of non-intubated patients with AHRF and a PaO_2/FiO_2 ratio of ≤300 mmHg, the increase of HFNC flow rates progressively decreased inspiratory effort and improved lung aeration, dynamic compliance, and oxygenation while most of the effect on inspiratory workload and CO_2 clearance was already obtained at the lowest flow rates [8].

Since HFNC may not be beneficial and successful in all patients with ARHF/ARDS, someone should be cautious as when to terminate HFNC therapy and escalate ventilatory support since delays to identify failure of HFNC to improve patient symptoms in these might lead to delayed intubation and potentially worsen clinical outcomes. As such careful selection criteria by clinicians for initiation and termination of HFNC in AHRF/ARDS is quite important. Several variables like PaO_2/FiO_2 ratios and respiratory rates are helpful as important clinical criteria for the success of HFNC therapy. Needless to say, clinicians need established protocols to quickly identify patients who require NIPPV or intubation and mechanical ventilation when they recognize signs of HFNC therapy failure.

29.2.4 Coronavirus Disease-19

COVID-19 is a respiratory tract infection caused by a newly emergent coronavirus that was first recognized in Wuhan, China, in December 2019. Currently, the World Health Organization (WHO) has defined the infection as a global pandemic, and there is a health and social emergency for the management of this new infection. Oxygen supplementation is an essential component of the clinical management of COVID-19

patients. With its ability to provide stable and wide range of FiO_2s as well as some level of PEEP, HFNC can be an efficient intervention for oxygen supplementation in COVID-19 patients inside and outside the intensive care unit (ICU). Several case series indicated that 11–21% of COVID-19 patients received HFNC oxygen supplementation and were successfully treated with HFNC inside and outside the ICU [9, 10]. In a retrospective analysis of the outcomes of patients with COVID-19 with moderate-to-severe hypoxemic respiratory failure receiving HFNC therapy, the arterial oxygen saturation (SpO_2) to FiO_2 ratio improved from 123 on day 1 to 234 on day 7 along with drops in respiratory rate from 30 breaths/min to 26 breaths/min and in heart rate from 88 beats/min to 75 breaths/min. Also, using HFNC resulted in significant improvements of chest x-ray scores from day 1 to day 7. With the use of HFNC, 64% of COVID-19 patients were able to avoid invasive mechanical ventilation and the incidence of hospital-associated pneumonia was 2.9%. Available data strongly support the use of HFNC therapy in COVID-19 patients as it can reduce intubation rates and has the potential to reduce mortality and morbidity associated with it [11].

One possible concern for the use of HFNC in COVID-19 patients is the fact that HFNC is a potential aerosol-generating technique, with the consequent risk of infection. This risk can be minimized by placing patients in negative pressure rooms while receiving HFNC as well as by limiting the high-flow rates to the least efficient values (usually $\leq$30 L/min) and by placing surgical masks on the patient's face on top of the HFNC cannula.

29.2.5 Chronic Obstructive Pulmonary Disease

Phlegm retention and airway surface dehydration in chronic obstructive pulmonary disease (COPD) cause frequent exacerbations, lung function reduction, and poor life quality. HFNC is known to provide optimal levels of humidity and heat of inspired gas for superior conditioning of inspired gas and minimal secretions dryness and mucus formation.

Short-term use of HFNC in stable normo- and hypercapnic COPD patients is safe and can induce significant physiological improvements. Following 60 min of HFNC, significant decreases in $PaCO_2$, increases in PaO_2, increases in SpO_2, and decreases in alveolar to arterial oxygen pressure difference were observed in normocapnic and hypercapnic COPD patients [12].

In patients with COPD and chronic hypoxemic respiratory failure, the long-term effects of HFNC oxygen supplementation (approximately 6 h per day) include lower acute exacerbation of COPD, lower hospital admission rate, improved modified Medical Research Council scores from 3 months onward, improved St. George's Respiratory Questionnaire at 6 and 12 months, and improved $PaCO_2$ and 6-min walk test at 12 months with no significant effect on mortality [13].

29.2.6 Respiratory Compromise Secondary to Heart Failure

Due to its continuous positive airway pressure (CPAP) effect, HFNC may decrease preload reduction associated with beneficial hemodynamic and respiratory effects in adults with heart failure. HFNC flow rates greater than 20 L/min are associated with a decreased degree of inferior vena cava collapse. Other improvements associated with HFNC in heart failure patients include decrease respiratory rate and improvement in oxygenation [14].

29.2.7 Respiratory Compromise Secondary to Respiratory Infection

Research on the use of HFNC oxygen supplementation in the management of severe acute respiratory infection has been limited and scarce. In 2009 during the H1N1 outbreak, HFNC was utilized to improve oxygen saturation in adult patients who could not achieve $SpO_2 \geq 92\%$ with traditional oxygen therapy. HFNC was successful in 45% of

the patients, and there was no nosocomial pneumonia during treatment with HFNC [15].

The rate of success of HFNC in pneumonia patients with acute hypoxemic respiratory failure can reach 75%. Twelve hours of daily treatment with HFNC can significantly reduce the need for intubation and mechanical ventilation in these patients [16].

29.2.8 Pre-Intubation/Airway Instrumentation

Due to its ability to provide stable and high FiO_2 concentrations along with some level of PEEP via a nasal cannula, HFNC can improve the safety and success rate during manipulation of the airway (e.g., bronchoscopy, tracheal intubation) in both low- and high-risk critically ill patients.

HFNC at an FiO_2 of 50% and flow rates of 60 L/min that resulted in a median airway pressure of approximately 4 cmH_2O maintained higher PaO_2 values, higher arterial-alveolar oxygen tensions, and higher PaO_2/FiO_2 ratios compared to a venturi mask both during and after bronchoscopy in patients with $SpO_2 > 90\%$ while breathing room air [17].

Critically ill patients with respiratory failure undergoing intubation have an increased risk of hypoxemia-related complications. Delivering oxygen via HFNC through the nares has several theoretical advantages that may prevent or minimize the risks and complications associated with tracheal intubation. HFNC may be left in place, theoretically maintaining CPAP and thereby prolonging the non-hypoxemic apnea time. When compared to bag-valve-mask for preoxygenation before tracheal intubation of ICU patients with mild to moderate hypoxemic respiratory failure, HFNC was feasible and safe and did not result in significant decreases in SpO_2 during the apnea phase before intubation as with bag-valve-mask preoxygenation [18]. When compared to non-rebreathing bag reservoir mask, HFNC significantly improved pre-oxygenation and maintained SpO_2 at 100% during intubation of ICU patients whereas SpO_2 dropped to 94% with non-rebreather mask [19]. Data from a recent meta-analysis that included seven randomized controlled trial and 959 patients with acute hypoxemic respiratory failure indicated that patients preoxygenated with HFNC had significantly less desaturation than patients preoxygenated with conventional oxygen therapy (COT). Furthermore, HFNC resulted in lower risk of intubation-related complications than COT [20].

29.2.9 Post-extubation

After tracheal extubation and liberation from mechanical ventilation, patients are usually supported with conventional oxygen therapy and possibly noninvasive positive pressure ventilation when there is an element of hypercapnic respiratory distress. The role of HFNC oxygen supplementation has been evaluated in the post-extubation period to either prevent or treat post-extubation respiratory failure. In high-risk patients who developed hypoxemia after cardiothoracic surgery, HFNC was shown to be a valid treatment option and was not inferior to NIPPV in terms of treatment failure, reintubation rate, time to treatment failure, and mortality with the advantages of better tolerance and less pressure sores and skin breakdown [21].

Evidence suggests that HFNC should have a role in pre-emptive post-extubation management of ICU patients at risk of post-extubation hypoxemia. In these patients, HFNC led to higher PaO_2/FiO_2 ratios and less interface displacement causing the patients to desaturate less, undergo fewer reintubations, and require less ventilator support [22].

In post-extubation COPD patients who were recovering from an episode of acute hypercapnic respiratory failure of various etiologies, the application of HFNC post-extubation significantly decreased the neuroventilatory drive and work of breathing compared with conventional O_2 therapy [23].

29.2.10 Sleep Apnea

Obstructive sleep apnea (OSA) is attributed to upper airway collapse during sleep. Stenting of the airway with positive pressure can prevent collapse and prevent associated intermittent hypoxemia, neurocognitive dysfunction, and cardiovascular morbidity. Although CPAP is the most effective treatment, adherence is suboptimal. With its low CPAP/PEEP effect, HFNC can alleviate upper airway obstruction in children and to a lesser extent in adult. HFNC at flow rates of 15–20 L/min reduces arousals and apnea-hypopnea scores in OSA patients [24].

29.2.11 Immunocompromised Patients

When intubated for respiratory failure, immunocompromised patients have higher mortality rates than non-immunocompromised patients. Instrumentation of the trachea can significantly increase the risk for ventilator-associated pneumonia. Choosing the adequate oxygenation strategy in immunocompromised patients with acute respiratory failure is of utmost importance to minimize risks and complications and improve outcomes. When compared with standard oxygen, HFNC did not achieve significant reduction in intubation or survival rates in immunocompromised patients with hypoxemic acute respiratory failure despite that HFNC had significant physiological improvements [25]. HFNC oxygen supplementation can achieve similar outcomes but fewer complications compared to NIPPV in renal transplant recipients with AHRF secondary to severe pneumonia [26].

29.2.12 End-of-Life Care

Oxygen therapy is prescribed for patients with advanced cancer if it can alleviate the symptom of breathlessness. In advanced cancer patients with do-not-attempt-resuscitation order, treatment with HFNC oxygen supplementation yields improvements in 41% of patients, no changes but stable conditions in 44% of patients, and deteriorations in 15% of patients during therapy with an overall mortality of 55% [27]. Also, ICU patients with a do-not-intubate order can benefit from HFNC. Despite the high mortality in these patients, HFNC oxygen supplementation leads to significant improvements in oxygenation, decrease in respiratory rate, and degree of breathlessness and dyspnea [28].

29.2.13 HFNC in Emergency Departments

Dyspnea is one of the most common chief complaints upon presentation to emergency departments and acute hypoxemic respiratory failure is a major cause of admission to ICU. Usual first-line treatments of dyspnea and hypoxemia include standard oxygen therapies with nasal cannula or non-rebreathing masks. HFNC oxygen supplementation overcomes almost all the limitations of those devices especially in delivering of high and controlled FiO_2s. Although without pressure support, the set high flow during HFNC generates a low level of positive pressure in the upper airway and subsequent PEEP effect. Furthermore, HFNC continuously washes out dead space in the upper airways. All these physiological effects make HFNC therapy feasible for first line of intervention for acute respiratory distress in the emergency department. Early initiation of HFNC oxygen therapy in patients admitted to the emergency department for acute hypoxemic respiratory failure improves oxygenation, feeling of breathlessness, and the likelihood of recovery from respiratory failure compared to treatment with standard oxygen (61% vs. 15%) [29]. Also, HFNC is better tolerated in the ED with greater patient's comfort, no serious adverse events, and lower hospitalization [30].

29.2.14 Adverse Effects of HFNC

HFNC is not a panacea and it has many limitations (Table 29.2). Measures that help in overcoming the limitations of HFNC include applying the appropriate flow rates, closing the mouth as much as possible during therapy, and using

Table 29.2 Limitations of high-flow nasal cannula oxygen therapy

Expense and complexity	Air/O_2 blender and humidifier
	Requirement for high-pressure oxygen supply
Mobility	Limited ambulation
Leak compromising positive airway pressure effect	Inability to compensate for leaks
Variable nasopharyngeal airway pressure	Unstable and unpredictable CPAP effect
Potential for delayed intubation	Increased mortality

appropriate sized prongs (usually 50–75% of the nares opening). Inappropriate use of HFNC may lead to adverse outcomes particularly if HFNC is used longer than necessary and other noninvasive or invasive means of respiratory support are overlooked and delayed. Serious side effects are rare but individual cases of air leaks (e.g., pneumothorax, pneumomediastinum) have been reported mainly in children and young adults [31]. Subsequently the predictors of HFNC treatment failure are of special interest. The primary predictors include failure of respiratory rate to decrease, poor SpO_2, and persisting thoraco-abdominal asynchrony within the first 1-h post initiation of treatment [31].

29.3 Conclusion Discussion

High-flow nasal cannula oxygen therapy is a valuable clinical application alternative to conventional oxygen therapy for critically ill patients. A growing body of evidence suggests its feasibility and safety in treating patients with respiratory distress/failure, respiratory infection, COVID-19, obstructive airway diseases, and during the pre-intubation and post-extubation periods. HFNC should not be restricted to critical care units and can be of great help in emergency departments and general hospital wards.

Key Major Recommendations

- High-flow nasal cannula has several physiological advantages compared to traditional standard oxygen devices.
- High-flow nasal cannula oxygen supplementation is beneficial and safe in common clinical settings.
- Success of HFNC depends on the appropriate selection of patients, timing of therapy, and adequate knowledge of the adjustable HFNC variables.
- Clinicians should be vigilant as to when to terminate HFNC therapy and consider other forms of respiratory support.

References

1. Kallstrom T. ARC Clinical Practice Guideline: oxygen therapy for adults in the acute care facility – 2002 revision & update. Respir Care. 2002;47:717–20.
2. Ricard J, Boyer A. Humidification during oxygen therapy and non-invasive ventilation: do we need some and how much? Intensive Care Med. 2009;35:963–5.
3. Vargas F, Saint-Leger M, Boyer A, et al. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. Respir Care. 2015;60:1369–76.
4. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372:2185–96.
5. Ou X, Hua Y, Liu J, et al. Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials. CMAJ. 2017;189(7):E260–7.
6. Monro-Somerville T, Sim M, Ruddy J, et al. The effect of high-flow nasal cannula oxygen therapy on mortality and intubation rate in acute respiratory failure. Crit Care Med. 2017;45:e449–56.
7. Panadero C, Abad-Fernández A, Rio-Ramirez T, et al. High-flow nasal cannula for Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. Multidiscip Respir Med. 2020;15:693–8.
8. Mauri T, Alban L, Turrini C, et al. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med. 2017;43(10):1453–63.
9. Wang D, Hu B, Hu C. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with

COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
11. Patel M, Gangemi A, Marron R, et al. Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxaemic respiratory failure. BMJ Open Resp Res. 2020;7:e000650. https://doi.org/10.1136/bmjresp-2020-000650.
12. Vogelsinger H, Halank M, Braun S, et al. Efficacy and safety of nasal high-flow oxygen in COPD patients. BMC Pulm Med. 17(1):143–50.
13. Storgaard LH, Hockey HU, Laursen BS, et al. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. Int J Chron Obstruct Pulmon Dis. 2018;13:1195–205.
14. Roca O, Pérez-Terán P, Masclans JR, et al. Patients with New York Heart Association class III heart failure may benefit with high flow nasal cannula supportive therapy: high flow nasal cannula in heart failure. J Crit Care. 2013;28:741–6.
15. Rello J, Pe'rez M, Roca O, et al. High-flow nasal therapy in adults with severe acute respiratory infection: a cohort study in patients with 2009 influenza A/H1N1. J Crit Care. 2012;27:434–9.
16. Roca O, Messika J, Caralt B, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. J Crit Care. 2016;35:200–5.
17. Lucangelo U, Vassallo FG, Marras E, et al. High-flow nasal interface improves oxygenation in patients undergoing bronchoscopy. Crit Care Res Prac. 2012;2012:506382. https://doi.org/10.1155/2012/506382.
18. Simon M, Wachs C, Braune S, et al. High-flow nasal cannula versus bag-valve-mask for preoxygenation before intubation in subjects with hypoxemic respiratory failure. Respir Care. 2016;61(9):1160–7.
19. Miguel-Montanes R, Hajage D, Messika J, et al. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. Crit Care Med. 2015;43:574–83.
20. Fong KM, Au SY, Ng GWY. Preoxygenation before intubation in adult patients with acute hypoxemic respiratory failure: a network meta-analysis of randomized trials. Crit Care. 2019;23(1):319–30.
21. Stéphan F, Barrucand B, Petit P, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery. JAMA. 2015;313:2331–9.
22. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190:282–8.
23. Di Mussi R, Spadaro S, Stripoli T, et al. High-flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease. Crit Care. 2018;22(1):180–90.
24. McGinley BM, Patil SP, Kirkness JP, et al. A nasal cannula can be used to treat obstructive sleep apnea. Am J Respir Crit Care Med. 2007;176(2):194–200.
25. Lemiale V, Resche-Rigon M, Mokart D, et al. High-flow nasal cannula oxygenation in immunocompromised patients with acute hypoxemic respiratory failure: a Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study. Crit Care Med. 2017;45(3):e274–80.
26. Tu G, He H, Yin K, et al. High-flow nasal cannula versus noninvasive ventilation for treatment of acute hypoxemic respiratory failure in renal transplant recipients. Transplant Proc. 2017;49(6):1325–30.
27. Epstein AS, Hartridge-Lambert SK, Ramaker JS, et al. Humidified high-flow nasal oxygen utilization in patients with cancer at Memorial Sloan-Kettering Cancer Center. J Palliat Med. 2011;14:835–9.
28. Peters SG, Holets SR, Gay PC. High-flow nasal cannula therapy in do-not-intubate patients with hypoxemic respiratory distress. Respir Care. 2013;58:597–600.
29. Macé J, Marjanovic N, Faranpour F, et al. Early high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure in the ED: a before-after study. Am J Emerg Med. 2019;37(11):2091–6.
30. Lenglet H, Sztrymf B, Leroy C, et al. Humidified high flow nasal oxygen during respiratory failure in the emergency department: feasibility and efficacy. Respir Care. 2012;57(11):1873–8.
31. Nishimura M. High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. Respir Care. 2016;61(4):529–41.

Negative and Positive Noninvasive Pressure Ventilation

30

Giacomo Torretta, Maria Caterina Pace, and Marco Fiore

Abstract

Mechanical ventilation replaces or supplements the respiratory muscles' activity. Invasive mechanical ventilation is performed using a device that bypasses the upper airways, such as the nasal/orotracheal tube or the tracheostomy tube. Noninvasive mechanical ventilation (NIV), on the other hand, uses an interface that does not bypass the upper airways, thus avoiding some of the complications associated with intubation and improving patient comfort. Noninvasive ventilation techniques can be used using positive or negative pressure ventilators.

Negative pressure ventilation, most widely used during the first half of the twentieth century, had some disadvantages such as patient discomfort, difficult ventilation in subjects with variable anatomical conformations, and poor handling of the equipment. This led to a progressive replacement, after the 1970s, of negative pressure ventilators with new positive pressure ventilation systems.

Keywords

Positive pressure ventilation · Negative pressure ventilation · Interface · Acute respiratory failure

Abbreviations

ACPE	Acute cardiogenic pulmonary edema
ALI	Acute lung injury
ARF	Acute respiratory failure
CNEP	Continuous extrathoracic negative pressure
COPD	*Chronic* obstructive pulmonary disease
CPAP	Continuous positive airway pressure
NEEP	Negative end-expiratory pression
NIV	Noninvasive mechanical ventilation
NPV	Negative pressure ventilation
OSAS	*Obstructive* sleep apnea syndrome
PCV	Pressure-controlled ventilation
PEEP	Positive end-expiratory pression
PSV	Pressure support ventilation
VCV	Volume-controlled ventilation

G. Torretta · M. C. Pace · M. Fiore (✉)
Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_30

30.1 Introduction

Mechanical ventilation replaces or supplements the respiratory muscles' activity. Invasive mechanical ventilation is performed using a device that bypasses the upper airways, such as the nasal/orotracheal tube or the tracheostomy tube.

Noninvasive mechanical ventilation (NIV), on the other hand, uses an interface that does not bypass the upper airways, thus avoiding some of the complications associated with intubation and improving patient comfort.

Noninvasive ventilation techniques can be used using positive or negative pressure ventilators.

Negative pressure ventilation, most widely used during the first half of the twentieth century, had some disadvantages such as patient discomfort, difficult ventilation in subjects with variable anatomical conformations, and poor handling of the equipment. This led to a progressive replacement, after the 1970s, of negative pressure ventilators with new positive pressure ventilation systems.

30.2 Discussion and Analysis of the Main Topic

30.2.1 Negative Pressure Ventilation

Negative pressure ventilation (NPV) was the first ventilatory technique used in the clinical setting.

In the 1930s and 1940s it was used during polio epidemics. Subsequently it was replaced by orotracheal intubation and positive pressure ventilation due to the lack of protection of the airways and their collapse in patients with paralysis of the pharyngeal muscles.

In recent years, however, it has again been used successfully in patients with acute respiratory failure secondary to obstructive and restrictive lung and chest wall diseases.

The mechanism of action consists in artificially generating a sub-atmospheric pressure during inspiration: the negative pressure expands the chest wall and reduces the alveolar pressure; the pressure gradient between the opening of the airways and the alveoli generates an inspiratory flow which determines the alveolar ventilation. The exhalation occurs passively through the elastic forces of the respiratory system.

Negative pressure ventilator consists of a rigid container that encloses the chest wall and a pump capable of generating sub-atmospheric pressures inside the container.

There are three types of negative pressure ventilators:

- Steel lung, in which the rigid container (in plastic or aluminum) encloses the entire body surface of the patient with the exception of the head. It applies pressure changes to the entire body surface of the patient and requires only one seal with respect to the external environment.
- Poncho, consisting of a rigid support, which encloses the thoracic cage and abdomen of the patient and a nylon suit which, once worn, completely envelops the rigid support and is sealed at the neck, wrists, pelvis, and ankles of the patient.
- Armor, consisting of a hard plastic shell to be placed around the rib cage and upper abdomen, the only parts exposed to pressure variations.

The pumps can be located inside the container (steel lung) or outside (poncho and armor). These pumps allow a pressure-controlled and time-cycled ventilation so that the inspiratory flow and the tidal volume are not constant but depend on the mechanical characteristics (elastance and resistance) of the patient's respiratory system.

The pumps currently available allow you to set the level of sub-atmospheric pressure to be delivered during inhalation, the pressure level to be maintained inside the container during exhalation and the times of the respiratory cycle. Maintaining a sub-atmospheric pressure around the chest wall during exhalation (negative end-expiratory pression/NEEP) has physiological effects equivalent to those of PEEP (positive end-expiratory pression) during positive pressure ventilation.

The main factors determining the effectiveness of negative pressure fans are:

- Pump power (the maximum negative pressure generated varies from −60 to −100 cmH_2O depending on the models).
- Type of pressure wave generated by the pump (pumps that generate a square wave determine a tidal volume greater than those that produce a sine wave).
- Surface of the chest wall exposed to pressure changes.
- Number of seals required.

The following ventilation modes are currently possible:

- Negative cyclic pressure: ventilator delivers the sub-atmospheric pressure level set by the operator for the set time, during exhalation, which occurs passively, t pressure around the chest wall returns to the atmospheric level.
- Negative/positive pressure: ventilator delivers a sub-atmospheric pressure during inspiration and a positive pressure (greater than atmospheric pressure) during exhalation.
- Continuous extra thoracic negative pressure: ventilator delivers constant sub-atmospheric pressure throughout the respiratory cycle while the patient breathes spontaneously. The physiological effects of CNEP are similar to those of CPAP (continuous positive airway pressure).
- Negative pressure/NEEP: ventilator delivers two predetermined levels of negative pressure, respectively during inhalation and exhalation.

30.2.1.1 Clinical Applications

COPD (chronic obstructive pulmonary disease) patients can be treated with NPV by means of a steel lung in order to improve the ventilatory pattern (increase in tidal volume and minute ventilation, reduction in respiratory rate, reducing the work of the respiratory muscles) [1].

In patients suffering from neuromuscular diseases and chest wall deformities, the use of NPV allows you to rest the respiratory muscles, improve the breathing pattern, and slow the evolution of chronic respiratory failure [2].

Several studies show that the use of NPV is useful in pediatric patients and in neonatal respiratory distress syndromes.

30.2.1.2 Side Effects

The main side effect is the tendency to collapse of the upper airways: during NPV, the pressure inside the upper airways during inspiration becomes sub-atmospheric; this phenomenon facilitates the collapse of the upper airways at the pharyngeal level.

In addition, the patient's airways are not protected with a consequent potential risk of aspiration in case of vomiting.

30.2.2 Positive Noninvasive Ventilation

30.2.2.1 Background

The first work on the use of positive pressure ventilation dates back to 1912, when Bunnel [3] used a face mask to maintain lung expansion during thoracic surgery.

A series of studies conducted by Barach et al. [4] during the 1930s showed that continuous positive pressure (CPAP) applied using a face mask could be useful in the treatment of acute cardiogenic pulmonary edema and other forms of acute respiratory failure.

In the 1990s, the evidence of a reduction in complications related to nasal/orotracheal intubation [5] and the reduction of mortality and morbidity in selected patients with acute respiratory failure led to the explosion in the use of noninvasive ventilation methods.

30.2.2.2 Instruments and Techniques

The NIV uses an interface and different types of ventilation. Interfaces are devices that guarantee the connection between patient and ventilator allowing the release of pressurized gases in the airways. The available interfaces are nasal and oronasal masks, and helmets and nasal olives. Selecting an appropriate interface is crucial to the success of the NIV.

A *nasal mask* is a plastic device that is placed on the patient's nose. The tightness is guaranteed

by means of a soft cushion and anchoring systems (fastening straps). It is preferred in cases of chronic administration of NIV due to its high tolerability. It is not indicated in the early stages of ALI (acute lung injury) as the patient breathes through the open mouth.

Nasal olives are soft silicone or rubber plugs which, by not exerting any pressure on the root of the nose, can be useful in patients who develop irritation or skin ulcers on the face.

Oronasal masks cover both the nose and the mouth. They are preferred in the emergency department as dyspneic patients mostly breathe through the mouth. They interfere with language, with expectoration, and with nutrition, making them less tolerable in the long term. When the opening pressure of the upper esophageal sphincter (25.30 mmHg) is exceeded, the introduction of a nasogastric tube is recommended to reduce gastric distension. A particular type of oronasal mask is the total face mask which also incorporates eyes, avoiding pressure on the root of the nose, and, consequently, reducing the risk of skin ulcers.

The *helmet*, made of transparent latex free material, has a plastic ring that joins it to a soft collar that adheres to the patient's neck. It is secured to the armpits by padded straps. The patient has the possibility to drink through a straw and to feed on a liquid diet. Its advantages include good tolerability, even in pediatrics, low risk of skin lesions, and better comfort. The limitations of the helmet are the difficult assessment of the patient's effective ventilation. With this interface, in fact, a part of the tidal volume delivered by the ventilator stretches the helmet and does not participate in gas exchanges. The internal volume of the helmet varies between 6 and 8 L. Another limit is the possibility of rebreathing which, however, is modest if sufficient levels of gas flow are guaranteed.

30.2.2.3 Ventilation Modes in NIV

30.2.2.3.1 CPAP (Continuous Positive Airway Pressure)

CPAP is a ventilation that maintains a constant positive pressure in the airways without providing any assistance in the inspiratory phase to the patient. Mechanical ventilators or continuous-flow systems can be used for the application of CPAP. The continuous flow systems consist of flow generators (flowmeters), a reservoir able to reduce pressure oscillations within the system during the respiratory cycle phases and a PEEP valve able to ensure the maintenance of a constant pressure.

CPAP determines an improvement in oxygenation in many pathological conditions associated with the presence of edema or alveolar exudate. The improvement in oxygenation depends on various physiological mechanisms: the increase in functional residual capacity determined by CPAP with a reduction in the shunt rate and the shift of the patient's respiratory activity to a steeper area of the pressure/volume curve with reduced work by the patient, and, consequently, the oxygen consumption.

Furthermore, CPAP has important effects on heart; in fact, in patients with heart failure, positive intrathoracic pressure determines reduction of ventricle's transmural pressure and afterload.

30.2.2.3.2 PSV (Pressure Support Ventilation)

PSV is an assisted ventilation: the patient maintains the ability to initiate the breath by activating a trigger, which can be pressure or flow, and terminating it by a flow trigger. The main parameters to be adjusted are the pressure level of the inspiratory phase and the level of PEEP. Other parameters to set are the sensitivity level of the inspiratory trigger and the expiratory trigger (by varying the percentage of the peak inspiratory flow at which the ventilator opens the expiratory valve).

A typical starting setting in PSV during NIV is a supportive inspiratory pressure of 8–12 cmH_2O and a PEEP of 3–5 cmH_2O. In the presence of major air leaks, the cycling mechanism between inhalation and exhalation may be ineffective.

30.2.2.3.3 Controlled Mechanical Ventilation

Controlled mechanical ventilation can be pressure (PCV) or volume (VCV). In PCV the ventilator delivers sequences of high and low pressure

(PEEP). The tidal volume delivered to the patient will be the function of lung and rib cage compliance and flow resistance. In VCV, the tidal volume is set by the operator and the resulting pressures are a function of thoraco-pulmonary compliance.

30.2.2.4 Practical Applications

The starting point for the application of NIV is the identification of the patient suffering from signs and symptoms of respiratory distress:

- Increased dyspnea.
- Respiratory rate > 24 breaths/min.
- Use of accessory respiratory muscles and/or the presence of paradoxical breathing.
- Respiratory acidosis and/or hypoxemia ($PaCO_2$ > 45 mmHg with pH < 7.35 and/or PaO_2/FiO_2 < 200).

At the same time, patients with contraindications to NIV should be excluded:

- Patients in respiratory arrest.
- Severe hemodynamic instability (hemodynamic shock, ongoing myocardial infarction).
- Lack of protective reflexes in the upper airways (coughing and swallowing mechanism inadequate).
- Severe state of agitation or lack of cooperation.
- Traumatic or surgical facial injuries such as to prevent the application of the interface.
- Severe upper gastroesophageal bleeding.
- Undrained pneumothorax.
- Vomiting.

It is also necessary to identify NIV predictors of success or failure in order to recognize patients who may benefit from noninvasive ventilation and avoid unnecessary applications, delaying the start of invasive ventilation. The severity of acidosis can be a starting point. Brochard et al. [6] demonstrated that success in NIV in COPD patients is less likely with a more acidemic starting pH.

Once the patient has been identified, the choice of interface is essential for the success of NIV. The first choice falls on the face mask, which guarantees a more effective delivery of positive pressure in patients who, in the initial stages of respiratory distress, have mainly mouth breathing. The second choice, in case of intolerance to the mask or side effects due to decubitus, must be oriented on the helmet keeping in mind the problems related to the CO_2 rebreathing, especially in hypercapnic patients; therefore monitoring of patients undergoing NIV is essential for the achievement of clinical results and for improvement of symptoms.

Clinical parameters to be assessed will be the level of consciousness, reduction in expiratory work (respiratory rate, chest wall movement, use of accessory muscles) and patient-ventilator synchrony. Other instrumental parameters to be considered will be the tidal exhaled volume (more significant in patients undergoing NIV), pressure and flow curves, hemodynamic parameters (heart rate and arterial pressure), continuous ECG, and continuous oximetry blood gas analysis (basic and after 1–2 h).

If the response to NIV is insufficient, invasive mechanical ventilation should be considered early.

30.2.2.5 Indications

- COPD exacerbation.
- Asthma.
- Acute heart failure.
- Community-acquired pneumonia.
- Weaning from mechanical ventilation.
- Patient not to be intubated/not resuscitated.
- Post-operative.
- OSAS (obstructive sleep apnea syndrome).
- Trauma.
- Restrictive neurological diseases.

The major scientific evidence concerns the use of NIV in patients suffering from ALI caused by exacerbation of COPD. During NIV, the combination of external PEEP and inspiratory pressure support reduces the respiratory work, which is increased in the patient with COPD, counterbalancing the auto-PEEP.

The first study conducted by Meduri et al. [7] in 1989 shows improvements in respiratory exchanges

with reduction in intubation rates. In another randomized study, comparing NIV and conventional therapy, Kramer et al. [8] confirmed a reduction in the need to intubation and showed a significant improvement in PaO_2, heart rate, and respiratory rate, without a significant decrease in $PaCO_2$.

Several studies have shown a higher rate of NIV failure with the need to tracheal intubation in patients starting with more severe respiratory insufficiency ($PaCO_2 < 7.25$), without evidence of problems associated with late onset of invasive ventilation. Finally, emerges that NIV should be considered the first-line therapeutic option in patients with COPD exacerbations.

NIV is routinely used in patients with ACPE (acute cardiogenic pulmonary Edema) both in the emergency department and in the ICU.

In these patients, NIV can be delivered either by CPAP or by ventilatory assistance under pressure (PSV), offering a series of positive effects, such as reduction of preload with an improvement in heart failure, reduction in respiratory work, and related consumption oxygen secondary to an improvement in lung compliance. This improvement is secondary to an extrathoracic redistribution of lung water, an increase in residual functional capacity, and a shift on a steeper area of the pressure/volume curve.

Several studies such as a review and meta-analysis by Collins et al. [9] showed a reduction in the need for intubation and in mortality compared to medical therapy (oxygen, diuretics, and nitrates) associated with the early onset of NIV.

Recently, a prospective randomized study conducted by Gray et al. [10] (3CPO trial) did not demonstrate any difference in terms of the need for tracheal intubation and mortality despite the improvement in blood gas parameters and dyspnea.

The ERS/ATS clinical practice guidelines [11] recommend (not firmly) NIV as a preventive strategy for avoiding intubation in hypoxemic acute respiratory failure (ARF) only when performed by experienced teams in highly selected cooperative patients with community-acquired pneumonia or early ARDS without any associated major organ dysfunction.

Severe COVID-19 causes significant numbers of patients to develop respiratory symptoms that require increasing interventions. Initially, the treatment for severe respiratory failure included early intubation and invasive ventilation as this was deemed preferable to be more effective than noninvasive ventilation (NIV). However, emerging evidence has shown that NIV may have a more significant and positive role than initially thought. NIV includes continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP).

NIV can be reserved for patients with mild ARDS, with close monitoring, airborne precautions, and preferably in single rooms. In patients with suspected or diagnosed COVID-19 requiring NIV, helmets may be the best solution for CPAP or NIV because of minimal or no dispersion from leaks and easy to filter/scavenge exhausted gas. Due to the scarcity of this interface it is probable that traditional oronasal masks will be the most commonly used. In this case a suboptimal NIV set-up with interface with inappropriate seals and improper circuitry will not be tolerable. If NIV is the option, try "protective-NIV" with lower tidal volumes between 6 and 8 mL/kg [12].

Although there is a role for noninvasive respiratory therapie77s in the context of COVID-19 ARF, more research is still needed to define the balance of benefits and risks to treatment of COVID patients.

30.2.2.6 Adverse Events and Complications

The most frequent complications are related to the interface, the flow delivered by the ventilator, and the patient-ventilator interaction.

The various interfaces can cause, as a result of the pressure they exert on the face, discomfort, erythema, or ulceration.

Air leaks can cause conjunctival irritation, while the pressure generated by ventilation can cause pain in the sinuses and ears. Patient ventilator asynchrony is a common cause of NIV failure and is often related to patient agitation or excessive air loss.

30.3 Conclusion Discussion

The indication best supported by the literature for the use of NIV is acute respiratory failure linked to the exacerbation of COPD. After the COVID 19 pandemic, more and more evidence is accumulating to justify its use in patients with ALIs of other etiology.

Key Major Recommendations

- In patients suffering from neuromuscular diseases and chest wall deformities, the use of NPV allows you to rest the respiratory muscles, improve the breathing pattern, and slow the evolution of chronic respiratory failure.
- NIV should be considered the first-line therapeutic option in patients with COPD exacerbations.
- NIV can be reserved for patients with mild ARDS.
- NIV is routinely used in patients with ACPE.

References

1. Corrado A., Gorini M., Villella G, et al. Negative Pressure Ventilation in the treatment of acute respiratory failure: an old non-invasive technique reconsidered. Eur Respir J 1996; 9:1531–1544.
2. Corrado A, Gorini M. Negative-pressure ventilation: is there still a role? Eur Respir J. 2002;20:187–97.
3. Bunnel S. The use of nitrous oxide and oxygen to maintain anesthesia and positive pressure for thoracic surgery. JAMA. 1912;58:835–8.
4. Barach AL, Martin J, Eckman M. Positive-pressure respiration and its application to the treatment of acute pulmonary edema. Ann Intern Med. 1938;12:754–95.
5. Elliot MW, Steven MH, Phillips GD, et al. Noninvasive mechanical ventilation for acute respiratory failure. BMJ. 1990;300:358–60.
6. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbation of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
7. Meduri GU, Conoscenti CC, Menashe P, et al. Noninvasive face mask ventilation in patients with acute respiratory failure. Chest. 1989;95:865–70.
8. Kramer N, Meyer TJ, Meharg J, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 1995;151:1799–806.
9. Collins SP, Mielniczuk LM, Whittingham HA, et al. The use of noninvasive ventilation in emergency department patients whit acute cardiogenic pulmonary edema: a systematic review. Ann Emerg Med. 2006;48:260–9.
10. Gray A, Goodacre S, Newby DE, et al. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008;359:142–51.
11. Rochard B, Brochard L, Elliot MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.
12. Winck JC, Ambrosino N. COVID-19 pandemic and non-invasive respiratory management: every Goliath needs a David. An evidence based evaluation of problems. Pulmonology 2020;26(4):213–220.

Interface, Mouthpiece, Nasal Face and Alternative Interface

31

Anna Annunziata, Maurizia Lanza,
Antonio M. Esquinas, and Giuseppe Fiorentino

Abstract

In the last decades many new interfaces have been developed, and interfaces such as mouthpiece and armor have been further implemented thanks to the evolution of software. These advances have allowed the clinician today to have a wide choice, such as to be able to optimize the treatment for each individual patient and pathological condition. For those who approach noninvasive mechanical ventilation, it is necessary to be clear about all the possible interfaces and complications related to their use.

Keywords

Nasal mask · Oral mask · Total face mask · Helmet · Mouthpiece

Abbreviations

ALS	Amyotrophic lateral sclerosis
ARF	Acute respiratory failure
BDP	Bilateral diaphragmatic paralysis
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
DMD	Duchenne muscular dystrophy
EPAP	Expiratory positive airway pressure
IAPV	Intermittent abdominal pressure ventilation
MPV	Mouthpiece ventilation
NIV	Noninvasive ventilation

A. Annunziata (✉) · M. Lanza · G. Fiorentino
Unit of Respiratory Physiopathology, Monaldi Hospital, Naples, Italy

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

31.1 Introduction

The success of noninvasive ventilation (NIV) depends often from alternative external devices acknowledged as interfaces. Various types of interfaces can be used during NIV therapy – mouthpiece, nasal mask, face mask, and helmet mask. Patient comfort and enhanced compliance are critical factors in determining the NIV outcome. The impact of the device itself on the skin and the skin breakdown in this context is now recognized to be another clinically significant adverse effect of NIV [1]. Nasal bridge pressure ulcers linked to the use of NIV masks happen in 5–20% cases [2]. The role of therapeutic devices in the development of hospital-acquired pressure ulcers has been increasingly recognized over recent years. The development of pressure lesions can appear in prejudice to NIV and decide possible treatment failure. So, the choice of interface for each patient is crucial.

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_31

31.2 Discussion and Analysis of the Main Topic

31.2.1 Interfaces

31.2.1.1 Types of Interfaces

Different kinds of interfaces can be used during NIV treatment in the acute context. Deciding the fitting interface for patients, including ARF, requires thinking of patient preferences and tolerance, and discovering the exact size and fit is crucial to successful ventilation. Although interfaces are created from a variety of materials, the most usually used material is silicone; gel masks are prepared by some producers as well. The benefit of gel masks is that they accommodate to the silhouettes of the face. The availability of different types of interfaces makes the choice of appropriate interface for patients with ARF a significant challenge. Noninvasive support in the use of negative ventilation, CPAP, bi-level positive airway pressure, or other pressure- and volume-limited ventilatory modes is applied in patients with ARF. Unrelatedly of mode, however, a well-fit interface is necessary for all forms of NIV.

Nasal Mask. This mask covers the nose only and is preferable for long-term ventilation but has also been used for acute hypercapnic and hypoxemic respiratory failure. Preliminary studies with normal adults suggested that nasal ventilation is of limited effectiveness when nasal resistance exceeds 5 cmH_2O (Fig. 31.1a).

Oro-Nasal Mask (also known as a full-face mask). This mask incorporates the nose and mouth and rests on the mandible, and the surfaces of the nose and mouth (Fig. 31.1b).

Oral Mask. This mask fits inside the mouth connecting the teeth and lips and has a tongue

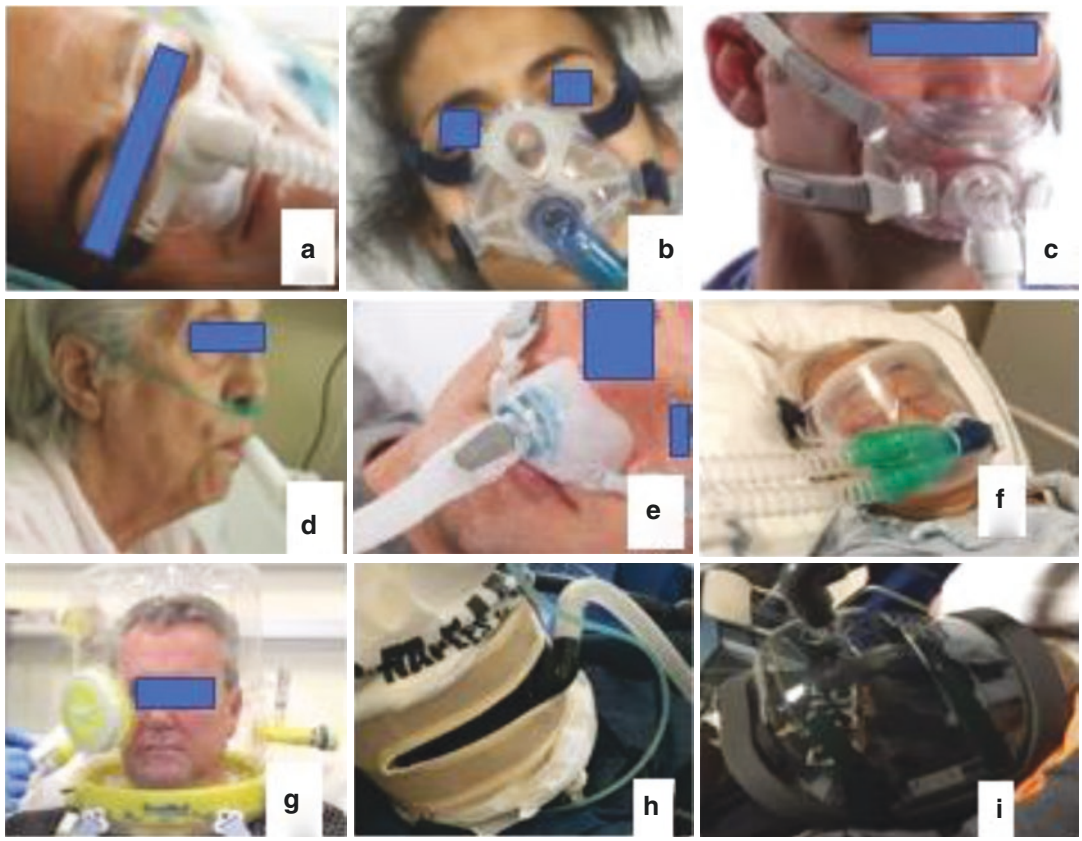

Fig. 31.1 Different interfaces. (**a**) Nasal mask, (**b**) oro-nasal mask, (**c**) oral mask, (**d**) mouthpiece, (**e**) nasal pillows, (**f**) full face mask, (**g**) helmet, (**h**) IAPV, (**i**) cuirass

controller to inhibit the tongue from blocking the airway passage. This type is not usual in practice (Fig. 31.1c).

Mouthpiece. A flexed mouthpiece fixed near the mouth by a flexible support arm is most useful for air supply. Many patients used a simple mouthpiece NIV since 1953. The Bennett Lipseal is made for fixing the mouthpiece in the mouth during sleep and closes the lips to avoid insufflated air from leaking out of the mouth. Patients described the mouthpiece as easy to use, especially during activities of daily living such as eating and speaking. Custom-molded bite-plates have also been made for mouthpiece NIV with or without retaining straps. Bach also described the usage of daytime mouthpiece NIV in combination with lip-covering custom-molded orthodontic bite plates for mouthpiece NIV use overnight. More recently, mouthpiece NIV was described to be as effective as a full-face mask NIV in decreasing inspiratory effort for treating ARF. Mouthpieces for daytime use may produce salivation, and long-term use can cause orthodontic malformations (Fig. 31.1d).

Nasal Pillow Mask. This mask fixes on the perimeter of the nose. This type of mask is regularly designated for persons who find nasal or oro-nasal masks painful or involvement of skin breakdown on the nasal bridge. Nasal pillows like nasal slings have less dead space than masks, are less likely to create claustrophobia, and permit the patient to wear glasses. Nasal pillows are used principally in stable patients with sleep-disordered breathing (Fig. 31.1e).

Total Face Mask. This mask covers the full face and is used mainly in patients with ARF (Fig. 31.1f).

Helmet. The helmet is a transparent shade that covers the complete head and face of the patient and has a rubber collar neck tape. It is used as an alternative for the oro-nasal mask in patients with acute hypoxemic respiratory failure or acute cardiogenic pulmonary oedema in some states. It was acquired to improve tolerability and decrease difficulties in patients with ARF on NIV [3]. It is not generally used in patients with acute hypercapnic respiratory failure (Fig. 31.1g).

IAPV: Intermittent abdominal pressure ventilation consists of an elastic inflatable bladder incorporated within a corset surrounding the abdomen. With bladder inflation by a ventilator, the abdominal content and diaphragm move upward, assisting expiration. With bladder deflation, inspiration occurs passively. IAPV facilitates diaphragmatic motion and may be particularly useful in patients with bilateral diaphragmatic weakness or paralysis (Fig. 31.1h).

Cuirass: The chest cuirass (a rigid case) and wrap-type structure (nylon poncho) are enclosures that allow application of negative pressure to the thorax. The effectiveness in producing tidal volume is correlated to the grade of body surface area that is exposed to negative pressure; it is larger with the iron-lung type than with the cuirass or poncho type of negative pressure ventilators (Fig. 31.1i).

31.2.2 Different Interfaces in the Acute Setting

In ARF, NIV effectiveness is more prominent than patient comfort, yet appropriate mask fitting and care are necessary to improve patient tolerance and, subsequently, to develop NIV outcome. Because there is no extensively ideal NIV interface, determining an interface requires a thorough evaluation of patient characteristics, ventilatory modes, and respiratory failure type. NIV can be used through a closed dual-limb circuit, an open single-limb circuit, or a closed single-tube circuit with a breath valve. A dual-limb circuit is formed by one tube for inhalation and another for exhalation, and a built-in exhalation port or filter for CO_2 elimination. Therefore, a non-vented mask is used to support the closed circuit. On the other hand, a vented mask should be used in open single-limb circuits. If a non-vented mask is utilized (open single-limb circuit), an additional exhalation valve in the circuit must be combined to allow CO_2 removal. Clinicians and respiratory therapists must be conscious of this life-threatening difference between ventilators because the use of a non-vented mask

in an open single-tube system without an exhalation port in the system can be tragic. It is worth considering that the interface itself acts as a dead space, which probably may improve the risk of CO_2 rebreathing and retention, especially in hypercapnic respiratory failure. The dead space is correlated to the internal volume of the interface. Nevertheless, an in vivo study revealed that the internal volume of the masks had no manifest short-term dead-space consequence on gas exchange, minute ventilation, or patient work [4]. Additionally, a different study that used computational fluid dynamics to describe pressure, flow, and gas composition during ventilation with the various interfaces showed that the adequate dead space is not correlated to the inside gas volume of the interface, which specifies that the internal volume is not a restrictive factor for the interface efficacy during NIV [5]. This recommends that the interfaces may be interchangeable in clinical practice with the difference of the helmet.

The decision of using just the interface is determined by the contour of the patient's profile, mouth, nose, breathing pattern, choice, and the experience of the medical staff. Two randomized controlled trials that confronted the oro-nasal mask with the nasal mask in subjects with ARF recorded no evidence that one type of interface is consistently more reliable than another in terms of clinical efficacy [6]. A recent study randomly selected 48 subjects with ARF into groups using an oro-nasal mask or a total face mask and observed responses for 24 h. At 6 h, the use of a full-face mask was significantly more effective in reducing $PaCO_2$ [7]. However, there was no difference between the two masks once subjects received the acute phase. Recognition and comfort were similar in both groups [7]; to increase comfort and reduce interface complexities of NIV in patients with ARF, the helmet was industrialized, which has the advantage of avoiding skin contact and hence improving patient tolerance independent of face morphology. The helmet has some intrinsic benefits as it allows patients to drink, communicate, and expectorate freely. Furthermore, it allows for the clearance of secretions and interaction with caregivers without removing the NIV interface. Studies have revealed that the patient tolerance scale in the helmet group is significantly more effective than with face masks [8].

The possible use of alternative interfaces such as mouthpieces and IAPVs must foresee experience with these interfaces, and the possibility of combining or alternating them to avoid the onset of decubitus requires careful choice of the candidate patient and close monitoring.

MPV. Several conditions may also be responsible for the failure of NIV, including claustrophobia, mask-induced skin lesions, rhinitis, and non-tolerance of pressure on the face. Other daytime NIV procedures should be considered in highly ventilator-dependent patients in addition to mask ventilation. Mouthpiece ventilation (MPV) is a type of noninvasive ventilation delivered via a mouthpiece. MPV was used for the first time on a ventilator-dependent polio patient. MPV, as we know it today, has been used for many years, and there is already evidence in literature documenting the efficiency of management and improved compliance by patients. Notwithstanding this, there is little data on the use of noninvasive mechanical ventilation with mouthpieces. Due to a recent evolution since 2013, mouthpiece ventilation modes are being introduced to commercially available portable ventilators, increasing the interest for this ancient modern interface [9]. For all clinicians working with mechanical ventilation, it is advantageous to have many treatment options available to sew the best suit for each patient.

Mouthpiece ventilation used a single-limb non-vented circuit ventilator in pressure-controlled or, more often, in the volume-controlled mode for permitting air stacking. The patient can catch mouthpiece ventilation, breathes inactively, using the set backup frequency on the ventilator, or he/she can actively trigger the breath, maintaining a part or all of the delivered volume. It is possible to use a simple single-tube circuit or a circuit with a valve. The valve is preferable for patients who cannot disconnect to exhale outside the circuit. Patients with the valve can stay connected for a long time in a row. The clinician should evaluate the patient's ability to synchronize with the mouthpiece held in the

mouth and to exhale outside the mouthpiece or not. Depending on the capacity to move the neck, the patient can constantly retain the mouthpiece between his/her lips or disconnect it for a variable time. The patient can self-sufficiently disconnect from the mouthpiece to speak, eat, cough, or call a family member. It presents no risk of skin breakdown and conjunctivitis, absence of claustrophobia, and lower probability of gastric distension. It is safer by permitting the use of glossopharyngeal breathing in the event of sudden ventilator failure or accidental disconnection from the ventilator [10]. Despite these obvious benefits, this modality is not frequently used. The same problem has been detected with a traditional interface in pediatric patients. Nose clips or nasal pledges can be used to avoid air leak through the nares for patients using lip-covering interfaces for mouthpiece NIV especially during sleep [11]. During the night, most patients use a mask because a mouthpiece needs cooperation and is uncomfortable. Air may also be swallowed and produce gastric enlargement. Mouthpiece and nasal NIV are open systems of ventilator support; the low-pressure alarms of ventilators not having mouthpiece NIV modes can often be sound. Back pressure from a 15 mm angled mouthpiece is sufficient to inhibit a low-pressure alarm set at 2 cmH_2O. The patient starts the inhalation by placing the mouth on the mouthpiece and making a slight negative pressure in the circuit by swallowing or gasping. Mouthpieces are very advantageous in adjunct daytime ventilation for patients suffering from neuromuscular diseases who cannot maintain adequate diurnal arterial blood gases without frequent recurrent periods of support [12]. Still, the risk of the use of MPV is that the patient may accidentally underventilate themselves because of the common disconnection from the mouthpiece [13]. The period of disconnection is probably the major limitation of this approach to NIV. The authors recognized that the periods of disconnection were connected with >5 mmHg $paCO_2$ increases and >2% spO_2 decreases, but no clinical complication happened before or after the monitoring period. Few patients accepted protracted disconnections without developing hypercapnia [13]. The most common type of asynchrony was an ineffective effort, also suggesting a need for improved trigger sensitivity. The recently introduced MPV software that allows insufflation to be triggered only by the positioning of the patient's lips appears to be an option for the patient with severe muscle weakness. Moreover, the software of many new ventilators is adding the mouthpiece mode. EPAP cannot be maintained for patients who use an open NIV system, and is indeed rarely, if ever, necessary for these patients. Apnea alarms, when existing, should be fixed at the maximum threshold to avoid avoidable start and discomfort. The usual ventilator mode used is assisted volume- and pressure-controlled with no EPAP, and the low-pressure alarm set to apnea minimum and maximum durations. The specificities of MPV, such as the intermittent disconnection of the patient and the presence of continuous leaks, may thus represent a challenge for turbine-based home ventilators. There is a great variance in the capacity of the different life support ventilators to deal with the rapidly changing respiratory load features that characterize MPV, which can be further accentuated according to the choice of ventilator settings. It is always indispensable to prudently observe the patient during the adaption phase since MPV needs true collaboration from the patient, and not all ventilators ensure rapid adjustment to the patient's respiratory acts [13]. However, due to its specific features and inconveniencies (air leaks, etc.), MPV must be used by professional hands and well-monitored. The use of MPV is likely limited to a few centers, for the longest time required to adapt and monitor the patient. In summary, the mouthpiece is a preferable and comfortable alternative to NIV, but more active participation is needed compared to the use of traditional masks.

Amyotrophic lateral sclerosis (ALS). Data in literature confirmed the usefulness of MPV. Bedard and McKim recently studied the utilization of daytime mouthpiece ventilation in an ALS population using 24-h NIV. Results demonstrate the effectiveness of mouthpiece ventilation as well as the importance of preserved bulbar function and ability to produce an acceptable peak cough flow with lung-volume recruitment

for survival. Mouthpiece ventilation is infrequently used in patients with ALS requiring continuous ventilatory support [12]. With adequate bulbar muscle function, mouthpiece ventilation was shown to be an effective alternative to tracheostomy [12]. The use of mouthpiece ventilation, combined with other interfaces, leads to an improvement in QoL and adherence to NIV. The patient who uses ventilation even during the night can alter an interface for sleeping and use MPV during the day; also, patients with skin lesions can benefit from using MPV.

31.2.2.1 Duchenne Dystrophy

The custom of mouthpiece ventilation in patients with DMD is documented in the literature. McKim discusses that 24 h NIV should be considered a safe alternative for patients with DMD because its use may obviate the need for tracheostomy in patients with chronic respiratory failure demanding more than nocturnal ventilation alone [13]. The authors examine the impact of diurnal mouthpiece intermittent positive pressure ventilation and conclude that daytime mouthpiece ventilation is safe, prolongs survival, and stabilizes vital capacity in Duchenne muscular dystrophy patients. As time passes, patients with DMD develop constant hypoventilation and need respiratory support 24 h a day; then, the mouthpiece can be very valued, principally in patients who use the NIV many hours a day and showing skin lesions, gastric distension, or eye irritation, sometimes alternating nasal and full-face masks. It is useful also to promote adherence to NIV.

31.2.2.2 Other Neuromuscular Disease

Bach and others have described a sizeable number of patients with neuromuscular diseases achieved long beyond the point of respiratory failure with 24 h NIV. Even patients before ventilated 24 h per day via a tracheostomy have been adapted to noninvasive mechanical ventilation with MPV [14]. Bach also describes noninvasive acute and long-term management of quadriplegia due to high spinal cord lesions. This includes full-setting, continuous ventilatory support by noninvasive intermittent positive pressure ventilation to support inspiratory muscles and mechanically assisted coughing to support inspiratory and expiratory muscles.

Bilateral diaphragmatic paralysis (BDP) is associated with dyspnea that worsens when the patient is recumbent, increased work of breathing, and exercise intolerance. With BDP progression, there is increasing ventilatory failure with hypoxemia and hypercapnia, which may further worsen due to atelectasis and ventilation–perfusion mismatch. There are reports showing that MPV is a clinically beneficial treatment to improve exercise tolerance and exercise-induced dyspnea in patients with BDP [15]. MPV can be useful for weaning from orotracheal tube or tracheostomy.

There are inadequate data on the usage of MPV in patient with Steinert dystrophy. Some authors described that it can be useful for Steinert patients (Fig. 31.1) who previously rejected the application of NIV for tightness, claustrophobia, and reduced compliance interface [16].

COPD. The benefits of noninvasive mechanical ventilation (NIMV) as first-line therapy in patients with exacerbations of COPD and hypercapnic respiratory failure are widely established. NIMV avoids intubation and is successful (>85%) especially in cases of mild to moderate acidosis with the aim to prevent further deterioration and the need for intubation [17].

Recent ERS/ATS guidelines on the management of noninvasive ventilation in acute respiratory failure (ARF), in fact, commend that there is no lower limit of pH below which a trial of NIMV is inappropriate in hypercapnic COPD exacerbation; however, its failure is directly related to severity of acidosis [18] so a close monitoring is necessary, and failure can often occur for poor tolerance to NIMV, mostly depending on the fit and shape of the interface used [19]. In approximately the large majority of cases, noninvasive positive pressure ventilation in ICU is administered through face or nasal masks, with some common disadvantages, such as air leaks, discomfort, pain, anxiety, secretions, skin lesions until to pressure necrosis, claustrophobia, asynchrony between the patient and the ventilator, and inability to eat, drink, speak, or cough.

Regrettably, all these adverse effects not infrequently lead to discontinuation of ventilation.

Intermittent abdominal pressure ventilation (IAPV). It consists of a corset with an elastic inflatable bladder that fits over the abdomen. The bladder is attached by a hose to a ventilator that give up to 2.5 L of air to the bladder and, thereby, to the abdominal wall. This raises the diaphragm to cause expiration below the functional residual capacity. Bach in 1990 described the use of intermittent abdominal pressure ventilator in ventilator-dependent traumatic quadriplegic patients, spinal cord injury, non-Duchenne myopathy, Duchenne muscular dystrophy, myelopathy, polymyositis, Friedreich's ataxia, and also employed it for long-term respiratory support. Intact mental status and bulbar musculature, absence of obstructive lung disease, and patients with traumatic high-level spinal cord injury are candidates to benefit from these techniques. New models avoid clothing taking on the corset buckles and are more comfortable [20]. They are now lightweight, suitable, easy to fit, and employ Velcro for fastening. The following IAPV parameters can be set: pressure inside the bladder, inspiratory time (real inspiratory time when the diaphragm moves down), frequency (respiratory rate), and rise time (time to inflate the bladder). The IAPV works well when a patient is in sitting position at an angle of 30° or greater and is optimal at 75°. IAPV is described in patients with a post-ischemic cervical myelopathy with success. IAPV can be used in patients who require NIV many hours a day [21]. Patients with gastric distension may benefit from the abdominal compression exerted by the device during the exhalation phase. Also, IAPV should be considered for patients with chronic disease who need to start NIV; it is helpful to promote a positive approach to NIV.

31.2.3 Negative Interface

Negative pressure ventilation (NPV) has played a crucial role in the history of ventilatory support for patients with respiratory failure in preventing endotracheal intubation in patients with acute exacerbation of COPD or neuromuscular disease. Jacket ventilators provided an inner framework of metal or plastic which was covered with a hermetic jacket with closures around the neck, arms, and thighs. The air in the jacket was alternatingly exiled, providing the ventilator action. Patients often desired assistance to put on and seal these jackets but they were proper for home use. Cuirass negative pressure ventilators were principally advantageous in children with neuromuscular disorders. Children had their own cuirass built from a plaster prototypical of the thorax and abdomen. This is important when there was severe thoracic scoliosis. The cuirass is a plastic model of the front and sides of the trunk; the edges were padded with air tight material and the cuirass attached to the patient with a back strap [22]. Pressure lesions with cuirasses were usual and new cuirasses were necessary as the patient grew. Cuirass ventilators were easy to wear and suitable for home use with a variety of negative pressure pumps which provided a preset negative pressure within the cuirass.

NPVs preserve physiological functions, such as speech, cough, swallowing, and feeding, and its major advantage is the prevention of endotracheal intubation and its related problems. The limitations are the lack of upper airway protection, particularly in comatose and/or neurological patients, that may end in aspiration, given the described consequence of NPV on the lower esophageal sphincter. Upper airway obstruction may occur or be amplified in unconscious patients, in patients with neurological disorders with bulbar dysfunction, and in those with sleep apnea syndrome. This can be overcome by the use of nasal CPAP, although in this situation, it may be more applicable to change to NPPV. Most of the descriptions of side-effects of NPV originated from stable, chronically ventilated patients: poor compliance, upper airway obstruction, and musculoskeletal pain. NPV has been associated with the possibility of rib fractures and pneumothorax. NPV can be efficaciously used in patients in whom excessive airway secretion or difficulty in wearing a mask avoid the application of NPPV. The iron lung is cumbersome and needs a large amount of space rather than problems

associated with NPV. The effectiveness of NPV depends on strict supervision by well-trained nurses and physiotherapists with significant skill with NPV. The major problems correlated to the support of patients with NPV by an iron lung are the transfer from the bed to inside the chamber of the tank ventilator and the access to patients for nursing practices during mechanical ventilation.

31.2.4 Problems Related to the Interface

31.2.4.1 Interface Type and Upper Airway Obstruction

It is vital to know the physiological effects of positive airway pressure applied through various interfaces on upper airway dynamics. To explain the consequences of different interfaces on upper airway patency, we need to review the difference between nose breathing and mouth breathing briefly. When breathing happens through the mouth, there is an improvement in upper airway resistance and an augmented propensity to acquire upper airway obstruction. Moreover, open-mouth breathing while awake decreases the retropalatal and retroglossal cross-sectional area and reduces the positive pharyngeal critical closing pressure during sleep. The oro-nasal mask applies pressure through the mouth and nose simultaneously, which may lead to a collapse of the airway. It is proposed that oro-nasal complimentary airway pressure therapy applies equal positive pressure in both nasopharyngeal and oropharyngeal compartments, which reduces the pressure gradient and allows gravity to displace the tongue and soft palate backward, resulting in airway obstruction [6]. The therapist needs to understand that the diversity in the efficacy of positive airway pressure applied via nasal and oro-nasal masks may determine the efficiency of NIV therapy, particularly in patients with hypercapnic obesity hypoventilation syndrome. Therefore, oro-nasal masks or face masks are favored in the acute settings; however, once the patient is stable, shifting to a nasal mask, if accepted, is suggested (Fig. 31.2).

31.2.4.2 Air Leaks

Air leaks are prevalent during NIV. There are two varieties of air leaks: intentional and unintentional leaks. Intentional leaks are intentionally produced during NIV when a one-limb circuit without an expiratory valve is present. An intentional leak is designed to bypass breathing again, having holes in the mask or circuit to allow for a leak proportional to their size, and set inspiratory pressure or typical inspiratory flow. Air leaks

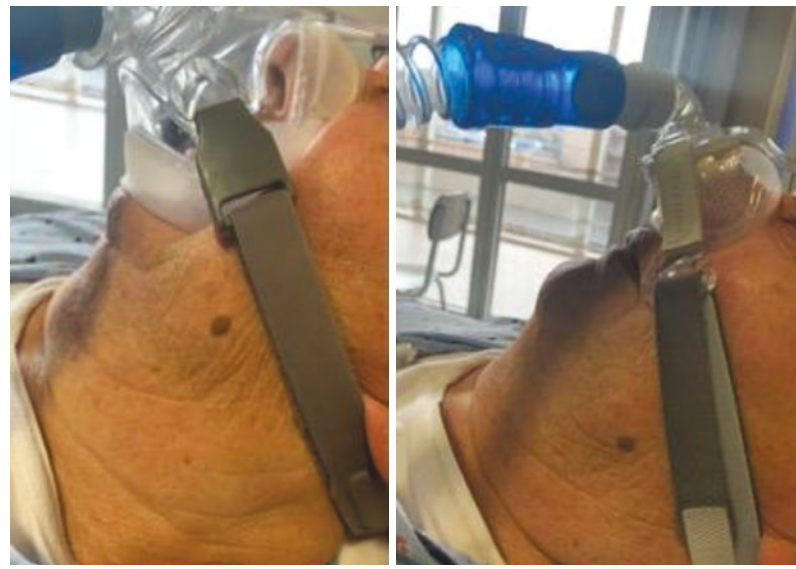

Fig. 31.2 Oronasal mask pressure on month

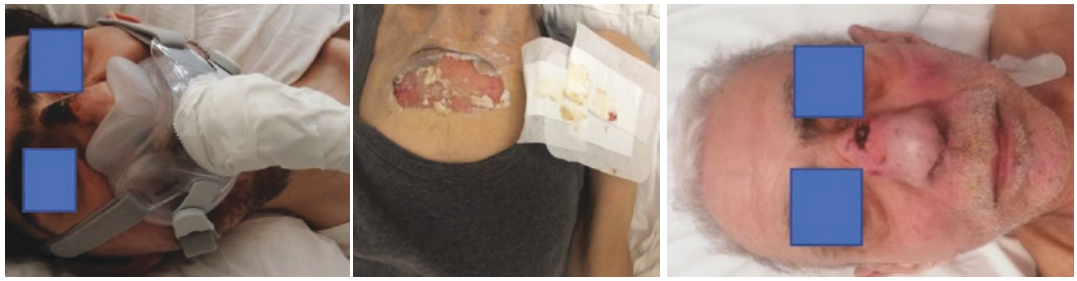

Fig. 31.3 Decubitus from positive and negative ventilation

depend on the sealing features of the interfaces; leakage is proportionally more prominent with a smaller face mask than with a larger mask or helmet [7]. Large air leaks are detrimental to the success of NIV as leaks decrease FiO_2 arterial oxygen saturation and improve in the automatic activation of the ventilator, thereby improving patient-ventilator asynchrony, which increases the risk of NIV failure. Additionally, air leaks can cause dry mouth and throat, conjunctivitis, or sleep disturbances [6]. In general, nasal masks tend to have more air leaks than face masks. Besides, the use of an oro-nasal mask reduces changes in relative humidity related to leaks from the mouth. Air leakage is negligible when a suitable interface for the NIV is chosen and installed [4]. Tight fitting of the interface can partly enhance the air outflow and patient asynchronous ventilator; yet, it should be done with caution as it raises the risk of facial skin discomfort and ulceration [4]. Also, it is essential to know that masks have different levels of loss. Therefore, each time activating sensitivity, pressure level, and rebreathing must be reduced when switching to a mask with a different degree of leakage.

31.2.4.3 Nasal or Oral Dryness and Nasal Congestion

Nasal or oral dryness and nasal congestion are typical during NIV. These side effects can be correlated to air leaks and the interface utilized. Previous studies have explained that during NIV, nasal or oral dryness and nasal congestion influence 10–20% and 20–50% of subjects, particularly when a nasal mask is applied [5]. Progressive nasal mucosal dryness releases inflammation mediators that increase nasal congestion and hence nasal obstruction, which decreases tidal volume and patient comfort. Strategies for reducing airway dryness and congestion during NIV mainly focus on reducing air leak [23].

31.2.4.4 Decubitus

With extensive use of NIV, nasal skin lesions such as erythema and ulcers may develop at the site of mask contact. Nasal erythema or ulcers account for a significant portion of interface developments during NIV reported to occur in 5–30% of patients, which increases to 50% of patients after a few hours; skin lesions may occur in almost 100% of patients after 48 h of NIV with a mask [23]. Although the nasal bridge is the most delicate area, skin lesions can also appear on other facial areas, in particular, over the zygomatic bone. There are many types of skin lesions, ranging from slight redness over the nasal bridge to open ulcers. The evolution of skin abrasions or necrosis is an influential factor that limits the tolerance and continuance of NIV. There is also evidence of decubitus during negative ventilation (Fig. 31.3).

31.3 Conclusion Discussion

The decision of the proper interface is crucial for the success of NIV therapy. Most interfaces are presented with a fitting measure to help choose the exact size to improve tolerance and bypass complications. Settling the interface too tightly minimizes patient tolerance and raises the risk of facial skin breakdown; consequently, if the headgear is fixed, it should be reasonable to permit

two fingers beneath it. If the patient does not tolerate the interface or if a significant leak is identified, a distinct interface should be utilized to avoid NIV failure. When a different interface is used, trigger sensitivity, pressurization level, and compatibility with the circuitry must be verified. Once the patient's health is stable, a nasal mask can be tried because it is less claustrophobic and is correlated with a lower risk for skin problems. Knowledge of the risk factors associated with pressure ulcer development is the key to the success of prevention strategies. The risk of developing pressure ulcers should be assessed in patients in all care settings within the first 6 h after patient admission. Routine assessment of the skin (check every 3–4 h) and possibility of pressure ulcers, regular pressure support, and skin-protective tactics should be involved in the routine use of NIV to decrease discomfort and the occurrence of soft tissue injury. Rotation or alteration of the interface and the interruption of usage duration of NIV may help to prevent face lesions.

Key Major Recommendations

- The decision of the proper interface is crucial for the success of NIV therapy.
- Non-optimal interface can produce several leaks and can produce patient intolerance.
- We can also think a negative or positive abdominal ventilation if the patient is intolerant.
- To avoid decubitus, we can use an interface alternation.
- When a different interface is used, trigger sensitivity, pressurization level, and compatibility with the circuitry must be verified.

Conflict of Interest The authors declare no conflict of interest.

References

1. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: non-invasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426.
2. Yamaguti WP, Moderno EV, Yamashita SY, Gomes TG, Maida AL, Kondo CS, et al. Treatment-related risk factors for development of skin breakdown in subjects with acute respiratory failure undergoing non-invasive ventilation or CPAP. Respir Care. 2014;59(10):1530–6.
3. Munckton K, Ho KM, Dobb GJ, Das-Gupta M, Webb SA. The pressure effects of facemasks during non-invasive ventilation: a volunteer study. Anaesthesia. 2007;62(11):1126–31.
4. Schettino GP, Chatmongkolchart S, Hess DR, Kacmarek RM. Position of exhalation port and mask design affect CO_2 rebreathing during noninvasive positive pressure ventilation. Crit Care Med. 2003;31(8):2178–82.
5. Fodil R, Lellouche F, Mancebo J, Sbirlea-Apiou G, Isabey D, Brochard L, et al. Comparison of patient-ventilator interfaces based on their computerized effective dead space. Intensive Care Med. 2011;37(2):257–62.
6. Sadeghi S, Fakharian A, Nasri P, Kiani A. Comparison of comfort and effectiveness of total face mask and oronasal mask in noninvasive positive pressure ventilation in patients with acute respiratory failure: a clinical trial. Can Respir J. 2017;2017:2048032.
7. Liu Q, Gao Y, Chen R, Cheng Z. Noninvasive ventilation with helmet versus control strategy in patients with acute respiratory failure: a systematic review and meta-analysis of controlled studies. Crit Care. 2016;20:265.
8. BaHammam AS, Singh T, George S, Acosta KL, Barataman K, Gacuan DE. Choosing the right interface for positive airway pressure therapy in patients with obstructive sleep apnea. Sleep Breath. 2017; https://doi.org/10.1007/s11325-11017-11490-11329.
9. Pinto T, Chatwin M, Banfi P, Winck JC, Nicolini A. Mouthpiece ventilation and complementary techniques in patients with neuromuscular disease: a brief clinical review and update. Chron Respir Dis. 2017;14(2):187–93. https://doi.org/10.1177/1479972316674411.
10. Garuti G, Nicolini A, Grecchi B, Lusuardi M, Winck JC, Bach JR. Open circuit mouthpiece ventilation: concise clinical review. Rev Port Pneumol. 2014;20(4):211–8. https://doi.org/10.1016/j.rppneu.2014.03.004.
11. Fiorentino G, Esquinas AM. Home ventilator performances with mouthpiece ventilation: does resistance change effectiveness? Clin Respir J. 2018;12(4):1765–6. https://doi.org/10.1111/crj.12676. Epub 2017 Aug 6
12. Bédard ME, Douglas A, McKim DA. Daytime mouthpiece for continuous noninvasive ventilation in individuals with amyotrophic lateral sclerosis. Respir Care. 2016;61:1341–8.
13. Bach JR, Alba AS, Saporito LR. Intermittent positive pressure ventilation via the mouth as an alternative to tracheostomy for 257 ventilator users. Chest. 1993;103:174–82.
14. McKim DA, Griller N, LeBlanc C, Woolnough A, King J, et al. Twenty-four-hour non-invasive ventilation in Duchenne muscular dystrophy: a safe alternative to tracheostomy. Can Respir J. 2013;20:5–9.

15. Koopman M, Vanfleteren LEGW, Steijns S, Wouters EFM, Sprooten R. Increased exercise tolerance using daytime mouthpiece ventilation for patients with diaphragm paralysis. Breathe (Sheff). 2017;13(3):225–9. https://doi.org/10.1183/20734735.005817.
16. Annunziata A, Fiorentino G, Esquinas A. Effect on lung function of mouthpiece ventilation in Steinert disease. A case report. Acta Myol. 2017;36(1):33–5.
17. Rochwerg B, Brochard L, Elliott M, Nava S, et al. Official ERS/ATS Clinical Practice Guidelines: noninvasive ventilation for acute respiratory failure. ERJ. 2017;50:1602426.
18. Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, et al. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbations. ERJ. 2005;25(2):348–55.
19. Nava S, Navalesi P, Gregoretti C. Interfaces and humidification for non-invasive ventilation. Resp Care. 2009;54(1):71–84.
20. Bach JR, Alba AS. Intermittent abdominal pressure ventilator in a regimen of non-invasive ventilatory support. Chest. 1991;99(3):630–6. https://doi.org/10.1378/chest.99.3.630.
21. Banfi PI, Volpato E, Bach JR. Efficacy of new intermittent abdominal pressure ventilator for postischemic cervical myelopathy ventilatory insufficiency. Multidiscip Respir Med. 2019;14:4. https://doi.org/10.1186/s40248-019-0169-4.
22. Kwok H, McCormack J, Cece R, Houtchens J, Hill NS. Controlled trial of oronasal versus nasal mask ventilation in the treatment of acute respiratory failure. Crit Care Med. 2003;31(2):468–73.
23. Carron M, Freo U, BaHammam AS, Dellweg D, Guarracino F, Cosentin R, et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. Br J Anaesth. 2013;110(6):896–914.

Noninvasive Ventilation (NIV): Timing, Screening, and Follow-Up

32

F. Merciai, A. Marra, M. Vargas, C. Iacovazzo, and G. Servillo

Abstract

Noninvasive ventilation (NIV) is the support of mechanical ventilation through the upper airways of the patient, and its outcomes are influenced not only by diagnosis of respiratory failure but also by the timing of its use. It is essential to identify patients who may benefit from the NIV and monitoring and following them to evaluate the therapeutic progress.

Keywords

Timing of application of noninvasive ventilation (NIV) · Use of NIV · Criteria for NIV Length of NIV · Monitoring and follow-up of NIV

Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary oedema
ETI	Endotracheal intubation
FiO_2	Fraction of inspired oxygen
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation
NPPV	Noninvasive positive pressure ventilation
OHS	Obesity hypoventilation syndrome
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PAV	Proportional assist ventilation
PEEP	Extrinsic positive end expiratory pressure
PSV	Pressure support ventilation
RCT	Randomized controlled trial
SaO	Oxygen saturation

F. Merciai · A. Marra (✉) · M. Vargas · C. Iacovazzo
G. Servillo
Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy
e-mail: servillo@unina.it

32.1 Introduction

Noninvasive ventilation (NIV) refers to the support of mechanical ventilation through the upper airways of the patient using masks and other devices. NIV differs from invasive mechanical ventilation (IMV) that bypass airways with endotracheal intubation (ETI) or laryngeal mask or tracheotomy. Compared with invasive mechanical ventilation, NIV achieves the same physiological benefits of reduced work of breathing and improved gas exchange [1].

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_32

Furthermore, NIV avoids the complications of intubation and reduces the risk of ventilator-associated pneumonia, especially in patients who are immunosuppressed or have other comorbidities [1].

NIV techniques can be performed using positive or negative pressure ventilator. Noninvasive positive pressure ventilation (NPPV) is defined as any form of ventilatory support applied without the use of an invasive artificial airway. NPPV can be applied with pressure generators or volume preset ventilators. Continuous positive airway pressure (CPAP) maintains a constant positive pressure in the airways without any inspiratory support. Respiratory cycle is started and terminated by the patient spontaneously breathing. Breathing rate, flow, and tidal volume are defined by the characteristics of the respiratory system of the patient. In particular, CPAP is used as a valid presidium in the treatment of cardiogenic pulmonary oedema (CPE) and peri-operative acute respiratory failure (ARF). Pressure levels used to administer CPAP in patients with ARF are usually between 5 and 12 cmH_2O. Pressure-support ventilation (PSV) assists inspiration using a preset positive-pressure boost triggered by the patient. The operator decides the higher pressure of the inspiratory phase and extrinsic positive end-expiratory pressure (PEEP) level. The inspiratory pressure is delivered until the flow rate falls below a target pressure. In this way, the patient sets not only the breathing rate but also inspiratory and expiratory durations, the feature that distinguishes it from other ventilator modes. A typical starting setting during NIV provides an inspiration pressure of 8–12 cmH_2O and a PEEP of 3–5 cmH_2O. BiPAP ventilation is a combination of pressure support to reduce inspiratory work and PEEP to counterbalance intrinsic positive end-expiratory pressure. In this way it allows a greater reduction in work of breathing, especially in patients with chronic obstructive pulmonary disease (COPD). Proportional-assist ventilation (PAV) targets spontaneous inspiratory flow rate as a surrogate of patients' effort and might improve synchrony between patient and ventilator and tolerance in some patients. Although this mode might be more comfortable and needs fewer adjustments than some pressure-support modes, it is more complex to use than pressure-support ventilation and has not been widely adopted.

NPPV was applied not only to patients with chronic pulmonary disease but is also used to support those with ARF. The ARF included patients with exacerbation of COPD, CPE, pulmonary infiltrates in immunocompromised patients, and acute respiratory distress syndrome (ARDS), patients developing ARF in the peri-operative period, and those with either difficulty weaning from invasive mechanical ventilatory support or in whom ETI was considered inappropriate.

The endpoints of NPPV differ depending upon the clinical context. In acute exacerbation of COPD, the aim is to reduce CO_2 by unloading the respiratory muscles and augmenting alveolar ventilation, thereby stabilizing arterial pH. In EPA, the aim is to improve oxygenation, reduce work of breathing, and increase cardiac output. During episodes of hypoxemic ARF, the aim is to ensure an adequate PaO_2 until the underlying problem can be reversed. In patients with chronic ventilatory failure, the goal of NIPPV is to obtain sufficient oxygenation and/or CO_2 elimination reducing work of breathing. When used intermittently in patients with obesity hypoventilation syndrome (OHS), the aim is to limit sleep- and position-induced adverse changes in oxygenation and CO_2 elimination by stenting the upper airway.

The outcomes of NIV treatment are influenced not only by diagnosis of respiratory failure and patients' characteristics but also by the timing and the setting in which the patient is treated. The success of NIV depends on several factors, such as the type of ARF (hypoxemic or hypercapnic), the underlying disease, the location of the treatment, and the experience of the care team. Time is also important, both in terms of the moment at which NIV is applied and its total duration (i.e., the number of days of NIV and the daily hours of use).

32.2 Discussion and Analysis of the Main Topic

32.2.1 Timing

The success of NIV depends on several factors, such as the type of ARF (hypoxemic or hypercapnic), the underlying disease, the location of treatment, and the experience of the care team. Time is also important, both in terms of the moment at which NIV is applied and its total duration (i.e., the number of days of NIV and the daily hours of use). NIV may be used at different moments: to prevent the occurrence of impending (but not established) acute or post-extubation failure, at an early stage, when respiratory failure is already established, to avert the need for endotracheal intubation, and as an alternative to invasive ventilation at a more advanced stage of acute respiratory failure or to facilitate the process of weaning from mechanical ventilation. The duration and intensity of NIV strongly depend on the time it is instituted.

Early use of noninvasive ventilation is recommended because the opportunity for a successful start might be lost if delays arise and the patient's underlying disease progresses too far. NIV should be used as soon as respiratory failure is so severe that ventilator assistance is required.

The timing of the application of NIV is a critical factor. A longer delay between admission and NIV use was shown to be an independent risk factor for NIV failure in patients with hematological malignancy and hypoxemic ARF, probably due to the progression of the underlying disease [2]. Therefore, early use of NIV is recommended. It is also critical not to unduly delay the decision to intubate a patient with failed NIV because the risk of unanticipated respiratory or cardiac arrest could lead to increased morbidity and mortality.

Early use in patients with mild respiratory acidosis (as low as pH 7.30) and respiratory distress prevents further deterioration, avoiding endotracheal intubation and improving survival compared with standard medical therapy [3]. Because of the abrupt onset of ARF, its rapid progression and/or delays in receiving medical evaluation and appropriate treatment, some patients may worsen so much that mechanical ventilation becomes mandatory. However, ETI in such patients is not strictly required because of gasping for air, unconsciousness, or the need to protect the airway, NIV might still be advantageous compared with invasive ventilation. In a multicenter trial in patients with mild-to-moderate acidotic COPD, Plant et al. [3] noted that intubation and mortality rates were lower with NIV than with standard therapy alone, but subgroup analysis showed that these rates did not differ when pH at enrollment was less than 7.30. A study randomized patients with acute exacerbations of COPD to full-face mask PSV or standard therapy [4]. After 1 h of NPPV a significant decrease of breathing rate was observed, but not of arterial partial pressure of carbon dioxide ($PaCO_2$) levels. Both reported significant improvements in vital signs and a reduced rate of ETI and decreased length of hospital stay and in-hospital mortality for those treated with NPPV. Most of the complications in the control group were attributable to ETI and consecutive mechanical ventilation, but their mortality was higher (29%) than reported in other studies [5].

Very few studies have evaluated the use of NIV as a means to prevent and to treat post-extubation respiratory failure. A randomized trial was recently performed [6] to assess whether NIV is effective in preventing the occurrence of post-extubation failure in patients at risk. The study showed that the groups treated with NIV had a lower rate of re-intubation than did the groups in which standard therapy was used and intensive care unit (ICU) mortality was also reduced in the subgroup of hypercapnic patients treated with NIV. In conclusion, a promptly started use of NIV for at least 48 h in selected patients "at risk" may prevent post-extubation respiratory failure.

ARF in immunocompromised patients often signals a terminal phase of the underlying disease. Early use of NIV could be very helpful, as shown by randomized studies in intensive care units that. Antonelli et al. [7] compared NIV in facemask with standard treatment in patients receiving a solid-organ transplant and who had

hypoxemic ARF. NIV was associated with a significant reduction in the rate of ETI, ICU long of stay, mortality in ICU, and fatal complications.

The use of NIV has been suggested to avoid re-intubation in patients who show signs of "incipient" or even overt respiratory failure following extubation. In a more recent randomized, controlled trial [8] NIV was applied to patients who developed ARF within 48 h after extubation and compared with standard medical therapy. The patients were randomized to standard therapy alone or to NIV. The authors did not find any difference in re-intubation rate, hospital mortality rate, ICU stay, and hospital stay, despite there being a trend to a shorter duration of hospital stay in the NIV group.

There is a group of ventilated patients who require more gradual and longer withdrawal of mechanical ventilation. NIV has become a commonly used alternative to invasive ventilation. NIV is theoretically able to counteract several physiological mechanisms associated with weaning failure or difficulties. Extubation to NIV following a failed spontaneous breathing trial may be an attractive weaning strategy. The benefits of this approach include avoidance of the injurious effects of invasive mechanical ventilation and reduction in sedation requirements and a lower risk of nosocomial pneumonia. Weaning from mechanical ventilation is an important decision-making moment, the timing of which can influence the length of the stay and sometimes the prognosis. Unnecessary delays in the suspension of mechanical ventilation can prolong the stay in ICU, increasing the risks of complications and costs. Conversely, premature attempts can be a source of respiratory distress and delay the weaning process, hampering the resolution of ARF. Weaning should be started after resolution of the underlying problems responsible for ARF and when the patient has a good compensation of the basic acid balance, adequate oxygenation, low PEEP values, and sufficient strength of the respiratory muscles. In ventilator-dependent COPD patients, NIV has been shown to be as effective as invasive ventilation in reducing inspiratory effort and improving arterial blood gases [9].

As opposed to IMV, discontinuing and resuming ventilator support with NIV is not cumbersome and can be carried out several times a day. To prevent intubation and re-intubation, NIV is commonly applied intermittently for a variable number of hours, depending on various factors, such as the severity of the ARF and the patient's tolerance. It is worth noting that 3–4 days of NIV for less than 12 h/day are usually sufficient to reverse ARF; in patients with EPAC, NIV is commonly required for less than 6 h. Not surprisingly, the total duration of mechanical ventilation and the mean hours of daily application are longer when NIV is applied as an alternative to endotracheal intubation or in the weaning process. This may help to explain the higher rate of NIV failure due to discomfort and intolerance observed when NIV is used as an alternative to invasive ventilation [10].

Time is also a critical factor when assessing the success or failure of NIV because it is important not to unduly delay the decision to intubate a patient. Most of the studies evaluating predictors of NIV outcome suggest that patients who do not improve within a few hours should be considered for intubation. Changes in arterial blood gases (i.e., pH for hypercapnic respiratory failure and PaO_2/FiO_2 for hypoxic respiratory failure) have been considered the best predictors although respiratory rate has also been found to be a good predictor of response to NIV [11]. Despite prompt improvement soon after the institution of NIV, this treatment may fail in some patients later on.

32.2.2 Screening

It is essential that healthcare workers know how to identify patients who may benefit from the NIV and exclude those for whom the NIV would be useless or risky. The cause of respiratory failure is important in determining the likelihood of a successful outcome with NIV. Therefore, the starting point is to identify the patient with sign and symptoms of respiratory distress such as:

- Increased dyspnea (moderate to severe).
- Tachypnoea (>24 breaths per min in obstructive, >30 per min in restrictive).
- Signs of increased work of breathing, accessory muscle use, and abdominal paradox gas exchange.
- Acute or acute on chronic ventilatory failure ($PaCO_2 > 45$ mm Hg, pH < 7·35).
- Hypoxemia (partial pressure of oxygen $(PaO)_2$/fraction of inspired oxygen $(FIO)_2$ ratio < 200).

To start NIV, patient should be conscious and cooperative, although hypercapnic patients in narcosis may be an exception. During NIV, sedation should be performed with no/minimal respiratory depression and no/minimal impairment of the upper airway.

NIV should not be used in patients with respiratory arrest; unable to fit mask; medically unstable (blood pressure instability or arrhythmia); agitated, uncooperative; unable to protect airway; swallowing impairment; excessive secretions not managed by secretion clearance techniques; multiple (i.e., two or more) organ failure; recent upper airway or upper gastrointestinal surgery; hemodynamically unstable; and in patients who cannot protect airways.

At the same time, it is important to recognize the criteria for discontinuing NIV and proceeding with ETI in order to avoid dangerous delays. They are represented by:

- Patients' intolerance (discomfort, pain, or claustrophobia).
- Hemodynamic instability (hypotensive shock, uncontrolled cardiac ischemia, uncontrolled copious upper gastrointestinal bleeding).
- Failure to improve gas exchange and/or dyspnea.
- Deteriorating level of consciousness.

Identify the predictive factors of success or failure of the NIV can help to recognize the best candidates. Based on data from randomized controlled trials (RCTs), three temporal moments were identified: (1) immediate failure (within minutes to <1 h), (2) early failure (1–48 h), and (3) late failure (after 48 h) [4]. Immediate NIV failure refers to failure within minutes and not beyond the first hour. The causes are [4] weak cough reflex and/or excessive secretions, hypercapnic encephalopathy and coma, intolerance and psychomotor agitation, and "fighting with the machine": patient-ventilator asynchrony. Nearly 65% of NIV failures occur within 1–48 h of NIV use [4]. Most studies have focused on NIV use in either hypercapnic or pure hypoxic ARF. Oxygenation impairment, as shown by a decreased ratio of PaO_2 to FiO_2 (P/F ratio), is one of the most risk factors and predictors of NIV failure. Other hypoxic ARF risk indexes to consider are increased severity of disease and increased respiratory rate (>35 breaths/min). Instead hypercapnic ARF risk indexes are [4] poor nutritional status, increased heart rate, higher baseline C-reactive protein/white blood cell count, lower serum potassium, and airway colonization by non-fermenting gram-negative bacilli. Although the definition of late NIV failure has not been standardized; it is usually defined as failure that occurs 48 h after initiation of NIV, following an initial successful response. Late NIV failure has received less attention and has been studied mainly in hypercapnic ARF [12]. Actually, it occurs in a considerable subset of patients (about 15% of NIV failures). The occurrence of late failure in COPD patients admitted with hypercapnic ARF to ICUs when NIV was used >24 h was found to be associated with the presence of hyperglycemia and a lower pH at admission [12].

32.2.3 Follow-Up

Monitoring and follow-up of NIV patients is necessary to determine whether the method is able to achieve improvement in symptomatology, reduction of work of breathing, improvement of gas exchanges, good patient-ventilator synchrony, and patient comfort.

The patient can start NIV anywhere but as soon as possible should be transferred to UTI for continuous monitoring, until clinical stability is achieved. In fact, to use NIV, staff with

much experience, who are prepared to intubate promptly if goals are not met (i.e., hemodynamic stability, adequate oxygenation, good cooperation) [4]. Implementation of NPPV involves selecting the appropriate patient interface, connected to a ventilator and capable of applying positive pressure to the upper airway during an episode of acute respiratory failure. Six types of interfaces are commercially available: full-face (or oronasal) mask, total face mask, nasal mask, mouthpieces, nasal pillows or plugs, and a helmet.

Close follow-up is required to detect early and late signs of deterioration, thereby preventing unavoidable delays in intubation. It is therefore possible to evaluate the monitoring of gaseous exchanges by means of pulse oximetry and hemogasanalytic values obtained before the start of the NIV, after 1–2 h from the start and when indicated by clinical conditions. Physiological responses are evaluated by continuous electrocardiography, monitoring of breathing rate, blood pressure, and heart rate. Flow and pressure curves are used to detect the possible occurrence of patient/ventilator mismatching. The level of compliance, mental statucs, physical condition, oxyhemoglobin saturation, signs of air leakage around the mask, and respiratory rate were continuously monitored. Arterial blood gas analysis are performed at regular intervals to evaluate PaO_2/FiO_2, $PaCO_2$, HCO_3, SaO_2, electrolytes, and lactates.

The length of NIV is established according to clinical criteria and arterial blood gas values. Weaning from NIV is defined as complete independence from mechanical ventilation for at least 72 h. Initial success of NIV is defined as objective and subjective improvement in the first hours: objective criteria include the disappearance of respiratory distress signs, and the following changes from spontaneous breathing in these parameters (pH = 7·35, decrease in $PaCO_2$, with oxygen saturation $(SaO)_2$ [with or without oxygen] = 90%), while subjective criteria include improvement or absence of dyspnea, and each patient's comfort.

NIV should be discontinued in a timely manner if the patient is deteriorating on the basis of worsening pH and respiratory rate (for acute hypercapnic respiratory failure) or exhaled tidal volume > 9.5 mL/kg and heart rate, acidosis, consciousness, oxygenation, and respiratory rate score > 5 after 1 h (for hypoxemic respiratory failure).

32.3 Conclusion Discussion

NIV has an important role in the management of respiratory failure. The use of NIV in the treatment of acute respiratory failure related to COPD exacerbations is the best supported indication in the literature. Many other applications are undergoing further investigation.

Knowledge of NIV features and choice of the right patient in the appropriate setting and in the right time are key factors for the success of NIV. Every physician dealing with NIV should be aware of risk factors and closely monitor each patient for their presence or development to achieve a good response and to improve the prognosis. If a patient fails to improve sufficiently, prompt ETI should be performed without delay because there is an increased risk of morbidity and mortality with ETI after failed NIV. A satisfactory initial NIV attempt is not always a marker of a good outcome.

Key Major Recommendations

- NIV has an important role in the management of respiratory failure.
- The timing of the application of NIV is a critical factor in determining the likelihood of a successful outcome.
- The length of NIV is established according to clinical criteria and arterial blood gas values.
- Screening is essential to identify patients who may benefit from the NIV and exclude those for whom the NIV would be useless or risky.
- Monitoring and follow-up of NIV patients is necessary to determine whether the method is able to achieve improvement in symptomatology.

References

1. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374(9685): 250–9.
2. Adda M, Coquet I, Darmon M, et al. Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. Crit Care Med. 2008;36:2766–72.
3. Plant PK, Owen JL, Elliott MW. A multicentre randomised controlled trial of the early use of non-invasive ventilation in acute exacerbation of chronic obstructive pulmonary disease on general respiratory wards. Lancet. 2000;355:1931–5.
4. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
5. Lightowler JV, Wedzicha JA, Elliott MW, et al. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003;326:185–9.
6. Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173(2):164–70. Epub 2005 Oct 13
7. Antonelli M, Conti G, Bufi M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA. 2000;12:235–41.
8. Keenan SP, Powers C, McCormack DG, et al. Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. JAMA. 2002;287(24):3238–44.
9. Vitacca M, Ambrosino N, Clini E, et al. Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. Am J Respir Crit Care Med. 2001;164(4):638–41.
10. Squadrone E, Frigerio P, Fogliati C, et al. Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. Intensive Care Med. 2004;30:1303–10.
11. Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. Thorax. 2001;56:708–12.
12. Moretti M, Cilione C, Tampieri A, et al. Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax. 2000;55(10):819–25.

33

Ventilatory Modes: Neurally Adjusted Ventilatory Assist (NAVA)/Pressure Support Ventilation/Bi-PAP Mode/ Continuous Positive Airway Pressure

Carmine Iacovazzo, Claudia Veropalumbo, Annachiara Marra, Maria Vargas, and Giuseppe Servillo

Abstract

The purpose of this chapter is to describe the following ventilatory modes: neurally adjusted ventilatory assist (NAVA), pressure support ventilation, bi-PAP mode, and continuous positive airway pressure.

The aim is to analyze their main features, focusing on their indications, contraindications, and fields of application.

Keywords

Assisted ventilation · Neurally adjusted ventilatory assist (NAVA) · Pressure support ventilation (PSV) · BIPAP mode · Continuous positive airway pressure (CPAP)

Abbreviations

ARDS	Acute respiratory distress syndrome
BIPAP	Bilevel positive airway pressure
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
EAdi	Electrical activity of the diaphragm
FRC	Functional residual capacity
ICU	Intensive care unit
IMV	Intermittent mandatory ventilation
NAVA	Neurally adjusted ventilatory assist
OSA	Obstructive sleep apnea
PCV	Pressure Controlled Ventilation
PEEP	Positive end-expiratory pressure
PEEPH	PEEP high
PEEPL	PEEP low
PSV	Pressure support ventilation
WOB	Work of breathing

33.1 Introduction

The listed ventilatory modes need to be acknowledged from the clinicians who wish to refine their practice in the management of invasive and non-invasive ventilation.

C. Iacovazzo (✉) · C. Veropalumbo · A. Marra
M. Vargas · G. Servillo
Department of Neuroscience and Reproductive and Odontostomatological Sciences, Intensive Care Unit, University of Naples Federico II, Naples, Italy
e-mail: giuseppe.servillo@unina.it

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_33

Neurally adjusted ventilatory assist is a proportional ventilatory mode that uses the electrical activity of the diaphragm to offer a better patient-ventilator interaction, with a fine proportion to the patient effort.

Pressure support ventilation is a form of assisted ventilation in which the ventilator provides a constant pressure during inspiration once the patient has made an inspiratory effort.

Continuous positive airway pressure is a spontaneous breathing mode that take place at a certain level of positive pressure maintained throughout the whole ventilatory cycle, while in bilevel positive airway pressure the circuit switches between a high and a low airway pressure level.

33.2 Discussion and Analysis of the Main Topic

33.2.1 Neurally Adjusted Ventilatory Assist

Neurally adjusted ventilatory assist (NAVA) is a proportional ventilatory mode that uses the electrical activity of the diaphragm (EAdi) to offer ventilatory assistance in proportion to the patient's effort, in contrast to all other modes of ventilation, which adopt conventional pneumatic signals (flow, volume, and airway pressure). The diaphragm's electrical activity is considered the best available signal to assess the respiratory drive, to trigger on and cycle off the mechanical assistance, and to regulate its amount [1].

The motivation that led to the development of NAVA mode is essentially the necessity to reduce the occurrence of patient-ventilator asynchrony in patients receiving mechanical ventilation. It has been estimated that 25% of mechanically ventilated patients experience asynchrony events, increasing the length of ventilatory support [2, 3].

When a patient is not synchronized to the ventilator, this can potentially damage the diaphragm, resulting in a loss of force-generating capacity [4]. Moreover, when asynchrony is present, it is common practice in ICU settings to sedate the patient, to further reduce diaphragm activity.

In the NAVA mode, the inspiratory signal is detected using diaphragmatic electromyography through the Edi catheter, which is basically a nasogastric tube with miniaturized electrodes near the distal tip. The Edi catheter is inserted into the esophagus, and the electrodes are positioned at a level that is adjacent to the diaphragm. The values are reported in microvolts (μV) (Fig. 33.1).

Triggering of a breath occurs when a deflection greater than the set threshold (mostly 0.5 μV) occurs in the Edi waveform [5].

Delivery of pressure during inspiration is based on the strength of the Edi signal and the level of NAVA support ("NAVA level"), set by the operator together with the PEEP level. The NAVA level determines the amount of pressure delivered by the ventilator in proportion to the Edi. An estimated peak pressure that will be delivered during the breath is based on the following equation: [6]

$$\text{NAVA P peak} = \text{NAVA level} \times \left(\text{Edi peak} - \text{Edi min}\right) + \text{PEEP}$$

This means that the final mechanical assist delivered by the ventilator in NAVA will be proportional to the neural output as measured by the Edi signal: in this way, the support delivered by the ventilator is constantly under the control of the patient's respiratory center and corresponds, moment by moment and breath to breath, to the patient's ventilatory request.

Furthermore, the clinician has to set two different backup modes: the first one is a pressure support ventilation (PSV) that is activated in case the Edi signal is lost (e.g., displacement or deterioration of the catheter); the second one is a pressure controlled ventilation (PCV) backup mode that switches on in case of apnea (e.g., for excessive sedation, curarization) [6].

NAVA mode is specifically for use in patients who are capable of spontaneous breathing, that is, patients who have an Edi signal. Patients with the following conditions are excluded from the use of the NAVA mode:

Fig. 33.1 Maquet Critical Care, NAVA monitor [6]

- Heavily sedated and/or paralyzed.
- Damaged brain center.
- Absence of phrenic nerve activity.
- Diseases that prohibit neuromuscular transmission.
- Presence of apnea.

Further limitations are contraindications to Edi catheter placement, such as recent gastric or esophageal surgery and the presence of esophageal varicose veins.

Compared to other modes, NAVA shows the achievement of a better patient-ventilator interaction in terms of number of asynchrony events, but the ventilator-related complications (e.g., barotrauma, VAP), ICU mortality, ICU stay time, and hospital stay time are not significantly reduced, while the duration of ventilation can be even longer when NAVA is compared to PSV [7].

In conclusion, there is no direct evidence from human clinical trials that better patient-ventilator synchrony with NAVA results in better outcomes, but it remains a useful, promising tool.

33.2.2 Pressure Support Ventilation

Pressure support ventilation (PSV) is a form of assisted ventilation in which the ventilator provides a constant pressure during inspiration once it senses that the patient has made an inspiratory effort. Specifically, this ventilation mode is:

– *Patient-triggered*: Inspiration begins if a negative airway opening pressure (pressure-triggering) or a drop in flow (flow-triggering) is detected by the ventilator, of which the clinician has to set the sensitivity; this setting determines the patient's effort (in terms of pressure or flow change) that is required to trigger the ventilator.
– *Pressure-limited*: The ventilator pushes a volume of gas into the circuit, which leads to a rise in pressure until it reaches a certain value, set by the clinician.
– *Flow-cycled*: The ventilator switches into the expiratory phase once the flow has decreased to a predetermined value during inspiration, usually a certain percentage of the peak inspiratory flow.

While the operator sets the sensitivity level, inspiratory pressure (along with PEEP, if needed), and flow cycle criteria, the patient establishes the rate, inspiratory flow, and inspiratory time. Tidal volume is the result of pressure gradient (ΔP = Set pressure − EEP), patient effort, respiratory system compliance, and resistance.

It is important to recognize that, as a patient-triggered mode, pressure support should be used exclusively in patients with a reliable, steady spontaneous respiratory pattern, even though more recent ventilators provide backup ventilation (volume-controlled or pressure-controlled mandatory ventilation) if apnea occurs during PSV.

The role of PSV, alone or combined with other modes, is substantially to overcome ventilator system resistance and reduce work of breathing (WOB) in spontaneous breaths; PSV is the most commonly used mode during weaning from mechanical ventilation [8, 9].

33.2.3 Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is a spontaneous breathing mode that takes place at an operator-determined level of positive pressure, which is maintained throughout the whole ventilatory cycle. No mandatory breaths are delivered: CPAP provides patient-triggered and patient-cycled breaths.

CPAP can be provided as a standalone mode or in combination with other modes, like PSV or even intermittent mandatory ventilation (IMV). It can be applied by mask or via a cuffed endotracheal or tracheostomy tube; it may be provided through the ventilator or even using a high-flow gas source and a PEEP valve. Portable CPAP machines have also been developed for non-acute care setting and even in-home use.

With CPAP, the airway pressure is elevated during inspiration and expiration. In this way CPAP may both reduce the inspiratory WOB during spontaneous breathing, improve oxygenation, prevent alveolar collapse and atelectasis, and increase FRC and the lung surface area for gas exchange.

CPAP setting requires careful hemodynamic monitoring, as the augmentation of intrathoracic pressure decreases venous return, cardiac output, and blood pressure.

The CPAP mode is most commonly used to evaluate whether the patient can be weaned from the ventilator in spontaneous breathing trials but is also applied with the aim of improving gas exchange in patients with respiratory failure or preventing postoperative atelectasis [10]. Moreover, CPAP is considered as a first-line strategy in the management of patients with cardiogenic pulmonary edema (CPE), as it decreases the systemic venous return and left ventricle filling pressure, limiting pulmonary edema; CPAP has been proven to decrease the need for endotracheal intubation and hospital mortality in these patients [11].

Moreover, very high levels of CPAP for brief periods of time (e.g., 40 cmH_2O for 40 s) have been suggested as a part of recruitment maneuvers to open collapsed alveoli in selected patients with ARDS.

CPAP could be also used both in hospital and home settings, and in the treatment of obstructive sleep apnea (OSA): noninvasive CPAP delivered by oral or nasal mask at pressures in the range of 4–20 cmH_2O forces air into the upper airways to prevent soft tissues from collapsing, airway obstruction, and apnea [12]. If a CPAP of 20 cmH_2O fails to adequately control OSA, BIPAP may be employed.

33.2.4 Bilevel Positive Airway Pressure

Bilevel positive airway pressure (BIPAP) is another form of pressure ventilation in which the circuit switches between a high and a low airway pressure level in an adjustable time sequence.

The main operator controls are:

- FiO_2.
- PEEPH: High pressure level, set to achieve an inspiratory pressure of 5–15 cmH_2O above PEEPL and titrated to achieve adequate ventilation and reduced work of breathing.
- PEEPL: Low pressure level, initially set in the range of 5–10 cmH_2O and titrated to achieve desirable oxygenation, minimizing patient discomfort.
- TH: Length of time at PEEPH.
- TL: Length of time at PEEPL.

– Pressure support: Additional ventilator support can also be added in the form of PS at both pressure levels to augment the patient effort and can be left at 0 if no additional pressure is needed.

Inspiration is typically patient triggered; ventilation can be flow or time cycled. It is commonly used as a NIV mode through an oral or nasal mask, but it is often applied to intubated or tracheostomized patients.

Even though inspiration is patient triggered, the BIPAP mode cannot be considered as a pure assisted ventilation, since the transition between PEEPL and PEEPH inevitably generates a mandatory inspiration, similar to a PCV. During the mandatory inspiration, in opposition to PCV in which the expiratory valve is closed, the patient is able to exhale anytime. Similarly, when the pressure level changes from PEEPL to PEEPH, it provokes an expiration.

During the phases with no change in pressure level, technically the patient is essentially receiving a CPAP, with an established pressure value, high or low.

Conclusively BIPAP is a combination of a pressure-controlled ventilation and an assisted ventilation and, thanks to its diversified characteristics and setting chances, its fields of application are wide both in ICUs and non-critical settings for the treatment of acute or chronic respiratory failure linked to difference etiologies [13].

33.3 Conclusion Discussion

The ventilatory modes debated in this chapter offer a wide range of application in different clinical scenarios. Even if there is no direct evidence that better patient-ventilator synchrony with NAVA results in better outcomes, it remains a useful and fascinating tool. Instead PSV has a clear and established role in reducing WOB in spontaneous breaths, being frequently chosen for trials of weaning from mechanical ventilation, similarly to CPAP. Besides CPAP improves oxygenation, prevents alveolar collapse and atelectasis, and increases FRC and the lung surface area for gas exchange; furthermore CPAP is considered a first-line strategy in the management of patients with CPE, being able to decrease the need for endotracheal intubation and hospital mortality in these patients.

Key Major Recommendations

- If asynchrony occurs, NAVA is an advantageous tool to provide a better ventilator-patient interaction.
- PSV can be properly used in trials of weaning from mandatory ventilation.
- CPAP should be considered in the first place in CPE or OSA patients.
- If CPAP fails in case of OSA, BIPAP should be contemplated.

References

1. Lourenço RV, Cherniack NS, Malm JR, Fishman AP. Nervous output from the respiratory center during obstructed breathing. J Appl Physiol. 1996;21:527–33.
2. deWit M, Miller KB, Green KA, et al. Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med. 2009;37:2740–5.
3. Thille AW, Rodriguez P, Cabello B, et al. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med. 2006;32:1515–22.
4. Levin S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med. 2008;58:1327–35.
5. Jorens WV, Philippe G. Neurally adjusted ventilatory assist: a ventilation tool or a ventilation toy? Respir Care. 2011;56:327–35.
6. Education, Servo. NAVA tutorial. Maquet Critical Care.
7. Chen C, Wen T, Liao W. Neurally adjusted ventilatory assist versus pressure support ventilation in patient-ventilator interaction and clinical outcomes: a meta-analysis of clinical trials. Ann Trans Med. 2019;16
8. Esteban A, Alia I, Ibañez J, et al. Modes of mechanical ventilation and weaning: A National Survey of Spanish Hospitals. Clin Invest Crit Care.
9. Botha J, Green C, Carney I, Haji K, Gupta S, Tiruvoipati R. Proportional assist ventilation versus pressure support ventilation in weaning ventilation: a pilot randomised controlled trial. Crit Care Resusc. 2018;20(1):33–40.
10. Ireland CJ, Chapman TM, Mathew SF, Herbison GP, Zacharias M. Continuous positive airway pressure (CPAP) during the postoperative period for prevention of postoperative morbidity and mortality fol-

lowing major abdominal surgery. Cochrane Database Syst Rev. 2014;
11. Bello G, De Santis P, Antonelli M. Non-invasive ventilation in cardiogenic pulmonary edema. Ann Transl Med. 2018;6
12. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, Iber C, Parthasarathy S, Quan SF, Rowley JA. Positive Airway Pressure Titration Task Force and Medicine. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. American Academy of Sleep. J Clin Sleep Med. 2008;4:157–71.
13. Paula G. David-João, Murilo H. Guedes, Álvaro Réa-Neto, Viviane B. de Oliveira Chaiben, Cristina P. Baena, Noninvasive ventilation in acute hypoxemic respiratory failure: a systematic review and meta-analysis. J Crit Care 2019;49:84–91.

34 Pulmonary Function Measurement in Noninvasive Ventilatory Support

Mohammed AlAhmari

Abstract

It is essential to investigate pulmonary function measurements in the management of patients with respiratory conditions or diseases. The measurements help in diagnosis, monitoring response to treatment, and can provide assistance in guiding clinical decisions. Noninvasive ventilation (NIV) is commonly used for respiratory failure. Delay in assessing and monitoring NIV failure can lead to fatal outcomes. Therefore, pulmonary function tests are crucial in monitoring lack of responsiveness to NIV, respiratory failure progression, or complications related to either underlying pathology or machine. Patient-ventilator synchrony is an important issue affected by machine performance and its interface and patient characteristics. Accurate recognition and management for asynchrony require proper bedside assessment of ventilator graphics and a patient's clinical observation.

Keywords

Noninvasive mechanical ventilation · Patient-ventilator interaction · Asynchrony · Leak compensation · Failure

Abbreviations

ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
NIV	Noninvasive mechanical ventilation
O_2	Carbon dioxide
$PaCO_2$	Arterial carbon dioxide tension
PEEP	Positive end-expiratory pressure
PEEPi	Intrinsic positive end-expiratory pressure
VTE	Expiratory tidal volume

34.1 Introduction

NIV can be a life-saving modality for patients with acute and chronic respiratory failure. The goal is to reduce the work of breathing by unloading the respiratory muscles and improving gas exchange [1].

There is clear evidence that patient-ventilator interaction is suboptimal, and the prevalence of asynchrony is common. Many factors lead to such suboptimal interactions such as clinical

M. AlAhmari (✉)
Dammam Medical Complex, Dammam Health Network—First Eastern Health Cluster, Dammam, Saudi Arabia

Respiratory Care Department, Prince Sultan Military College of Health Sciences, Dammam, Saudi Arabia
e-mail: m.alahmari@psmchs.edu.sa

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_34

observation, type of patients' conditions, detection methods, NIV mode types and settings, and type of asynchronies. Adverse effects resulting from patient-ventilator asynchrony include improper work of breathing, patient discomfort, increased length of hospital stay, and failure to wean of the ventilator, which may lead to higher mortality rate [2].

This chapter will review issues related to patient-ventilator interaction using NIV.

34.2 Discussion and Analysis of the Main Topic

34.2.1 Why Is Patient-Ventilator Interaction Important?

Understanding how a patient interacts with the NIV machine is important to highlight factors that may lead to improper management or failure of the NIV. These factors include the patient's condition and the process of the disease that affects respiratory function and related interventions [3]. Patient-ventilator interaction can be heavily affected by the type of interface, whether invasive or noninvasive tubes/masks. It is especially important clinicians respond properly and in a timely manner to these interactions. Table 34.1 lists several adverse consequences of patient-ventilator interaction [4].

Table 34.1 Adverse consequences of patient-ventilator interaction

Increased work of breathing
Poor ventilation and oxygenation
Respiratory muscle dysfunction
Lung hyperinflation and distention
Patient discomfort
Un-readiness for weaning
Excessive sedatives and neuromuscular blocking agents
Prolonged mechanical ventilation
Prolonged immobility and neuromuscular complications
Distress for family members
Miscommunication among team members

34.2.2 NIV and Patient-Ventilator Interaction

It has been shown that patient-ventilator asynchrony (PVA) is prevalent and common [3]. Dean Hess showed that the frequency of PVA is crucially correlated with patient comfort during NIV, and the greatest factor in PVI during NIV application was air leakage which showed that higher leakage led to more asynchrony, with high levels of pressure support [3]. Therefore, understanding an NIV machine and its specifications during NIV application is important. Some NIV machines have sufficient air leak compensation and others do not. It is critical that clinicians understand the triggering and cycling functions before switching to a different mask with different leak characteristics. Another factor addressed that may interfere with PVI during NIV was the sleep-wake cycle state and how it is related to over- and under-ventilation due to changes in ventilatory drive and airway resistance.

34.2.3 NIV Failure

NIV is the first line of therapeutic intervention in selected conditions and shows clear evidence of reducing the need for endotracheal intubation [1]. However, some patients fail NIV and reintubation becomes required. Randomized controlled trials showed significant reduction in intubation rate in patients with exacerbated COPD and acute cardiogenic pulmonary edema [5, 6]. However, 16% who received NIV were intubated. A French study showed 38% NIV failure rate with acute respiratory failure in a mixed population [7]. This proves that NIV is helpful in various populations [8]. Table 34.2 shows potential causes of NIV failure with some related to asynchrony [5].

Evidence showed successful NIV is associated with proper NIV tolerance [8] and good synchrony led to improved NIV comfort [9].

Table 34.2 Potential causes of NIV failure

Improper selection for the interface
Untrained and inexperienced clinicians
Selection of patient is poor due to degree of severity and diagnosis
Selection of ventilator type: leak compensation issue
Inappropriate ventilator settings

34.2.4 Asynchrony

The interface for NIV can be oronasal masks, nasal masks or pillows, total face masks, mouthpieces, or helmets [10]. It is common these interfaces promote air leaks compared to invasive ventilation interfaces, as seen in Table 34.3. In intensive care units (ICUs), the preferred NIV interface is the oronasal mask [11, 12].

The helmet acts as a semi-closed interface, which has a larger volume than the tidal volume. This results in increased inspired partial pressure of CO_2. Such increased PCO_2 in a helmet depends on the patient's production of CO_2 and the gas flow that flushes the helmet [13, 14]. Therefore, a minimum of 40–60 L/min gas flow (40–60 L/min) is needed to maintain a low inspired partial pressure of CO_2 [13]. The use of a helmet with pressure support ventilation compared with a face mask showed an increase in respiratory efforts and dyspnea, reduction in CO_2 clearance, and patient-ventilator asynchrony.

Rebreathing during NIV is another important issue. Potentially, it induces asynchrony because it increases respiratory drive and dyspnea. It has been shown that air hunger is detectable at an end-tidal PCO_2 4 mmHg and becomes intolerable with an increase in end-tidal PCO_2 of 11 mmHg [15].

Costa et al. performed a study that assessed synchrony with NIV using the oronasal mask and helmet as the interface [16]. The study showed that the helmet resulted in significant asynchrony compared to the face mask. One the issues that led to patient-ventilator asynchrony was the use of different interfaces for different ventilators. Mixing interfaces from one manufacture to another, trying to find best fit, does not work. In fact, this potentially creates an interface-ventilator mismatch. In such cases, it is important when switching masks to assess the leak characteristics in order to fix the trigger sensitivity and pressure settings and to avoid rebreathing.

Table 34.3 Potential consequences of NIV leaks

Poor efficiency of NIV
Patient intolerance
Frequent awakenings and sleep fragmentation
Patient-ventilator asynchrony

34.2.5 NIV Leak Compensation

Unfit interface or the ventilator manufacture type can cause failure of the NIV. There are two main differences between invasive interface and NIV with the airway sealed in the former and leaks occurring in the latter. NIV leaks led to significant patient-ventilator asynchrony which compromises respiratory pressures and the amount of delivered tidal volume [3]. The most common NIV asynchrony is auto-triggering. The auto-triggering is caused by the inability of the machine to detect the patient's trigger signal.

The two proper approaches to handle the leak is to deal with minimization and compensation for such NIV leaks. To minimize the leak, selection of the proper interface and fitting techniques should be carried out. To compensate for the leak, bilevel ventilators in critical care perform better in terms of synchrony due to automated leak compensation algorithm. These critical care ventilators allow the clinician to adjust and improve the patient-ventilator interaction, including trigger type, flow cycle, and sensitivity. Evidence suggests that the best option for better patient-ventilator synchrony is critical care bilevel ventilators with an NIV mode that provides better leak compensation.

34.2.6 Improvement of NIV Synchronization

There is less evidence supporting improved outcomes of patient-ventilator interaction with NIV. To improve outcomes of patient-ventilator synchronization, the clinician needs to perform

sufficient patient examination and ventilator assessment via waveforms. The clinician also needs to detect the type of triggering from ventilator waveforms: ineffective, double, auto, delayed, and premature cycling [3].

In order to improve the synchrony outcomes of NIV ventilators, there are several ways to first improve patient-ventilator interactions [3]. Properly fitting the interface is a crucial strategy in all synchronization methods. For trigger synchrony, PEEP can be used for auto-PEEP and adjustment for trigger sensitivity in order to balance between auto-triggering and trigger effort. For cycle synchrony, it is recommended to use time-cycled versus flow-cycled ventilation and adjust pressure support settings to minimal based on the clinical picture.

For flow synchrony, it is recommended to improve the synchrony by using volume-or-pressure targeted ventilation with proper adjustment to inspiratory pressure and flow and tidal volume accordingly. In addition, adjustment to the rise time can be helpful to comfort patients. The last strategy is NIV mode; in this method, it is recommended to use the backup rate in case of periodic breathing or apnea.

Ventilator adjustments are needed not only to improve the synchronization but also to improve patient underlying problems, as well. For many patients with NIV, the respiratory system goes through pathological and physiological changes that require frequent manipulations to ventilator settings in order to avoid improper ventilator-patient interactions.

34.2.7 Monitoring of Pulmonary Parameters

Data obtained by an NIV built-in algorithms device that describes patient's ventilation status is an important, useful tool in the assessment of the ventilation efficacy. Such data provide additional help to understand a lack of clinical improvement. NIV-ICU ventilators have shown more patient- ventilator asynchrony due to auto-triggering [17] created by a semi-open system and air leaks.

Expiratory tidal volume (VTE) is one of the main parameters to monitor NIV as it reads the patient's alveolar ventilation. Before initiating NIV, the VTE should be determined, can be calculated on the basis of ideal body weight and depends on disease or condition categories [18]. There is sufficient evidence that monitoring the rapid shallow breathing index (respiratory rate divided by VTE) may be a good NIV predictor of success.

Intrinsic positive end-expiratory pressure (PEEPi) is present in variable degrees in patients with moderate to severe COPD. Normally, it causes dynamic hyperinflation, lower respiratory compliance, and higher respiratory workload. During NIV, the presence of PEEPi can be investigated by inspection of the expiratory flow-time curve.

34.3 Conclusion Discussion

NIV is a supportive therapeutic option for the vast majority of ARF patients. The benefits of NIV application can be achieved only if adequate pulmonary function monitoring of patients is undertaken. The level of pulmonary function monitoring should depend on the severity of respiratory failure and the general condition of patients. The other pulmonary function parameter is the analysis of the ventilatory parameters: VTE, leak and I:E ratio, provided by the ventilator as pulmonary waveforms and numerical data. There is still evidence needed to improve patient-ventilator synchrony and to avoid NIV failure in early and late stages of a patient's condition.

Key Major Recommendations

- NIV is a crtucial ventilatory approach that show a strong relations with pulmonary function basic parameters (pressure/tidal volume and airflow) waveform.
- NIV response to early and late failure are related with patterns of patient-ventilator synchronization.

References

1. Rochwerg B, Brochard L, Elliott M, Hess D, Hill N, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426.
2. Epstein S. How often does patient-ventilator asynchrony occur and what are the consequences? Respir Care. 2011;56(1):25–38.
3. Hess D. Patient-ventilator interaction during noninvasive ventilation. Respir Care. 2011;56(2):153–67.
4. Pierson D. Patient-ventilator interaction. Respir Care. 2011;56(2):214–28.
5. Ram FS, Picot J, Lightowler J, Wedzicha JA. Noninvasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004;1:CD004104.
6. Weng C. Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. Ann Intern Med. 2010;152(9):590.
7. Demoule A, Girou E, Richard J, Taillé S, Brochard L. Increased use of noninvasive ventilation in French intensive care units. Intensive Care Med. 2006;32(11):1747–55.
8. Hess DR. How to initiate a noninvasive ventilation program: bringing the evidence to the bedside. Respir Care. 2009;54(2):232–43.
9. Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille A, Kossowsky M et al. Patient–ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med 2009;35(5).
10. Nava S, Navalesi P, Gregoretti C. Interfaces and humidification for noninvasive mechanical ventilation. Respir Care. 2009;54(1):71–84.
11. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J. 2010;36(2):362–9.
12. Kwok H, McCormack J, Cece R, Houtchens J, Hill NS. Controlled trial of oronasal versus nasal mask ventilation in the treatment of acute respiratory failure. Crit Care Med. 2003;31(2):468–73.
13. Taccone P, Hess D, Caironi P, Bigatello LM. Continuous positive airway pressure delivered with a "helmet": effects on carbon dioxide rebreathing. Crit Care Med. 2004;32(10):2090–6.
14. Mojoli F, Iotti GA, Gerletti M, Lucarini C, Braschi A. Carbon dioxide rebreathing during non-invasive ventilation delivered by helmet: a bench study. Intensive Care Med. 2008;34(8):1454–60.
15. Banzett RB, Lansing RW, Evans KC, Shea SA. Stimulus-response characteristics of CO_2-induced air hunger in normal subjects. Respir Physiol. 1996;103(1):19–31.
16. Costa R, Navalesi P, Spinazzola G, Ferrone G, Pellegrini A, Cavaliere F, et al. Influence of ventilator settings on patient-ventilator synchrony during pressure support ventilation with different interfaces. Intensive Care Med. 2010;36(8):1363–70.
17. Carteaux G, Lyazidi A, Cordoba-Izquierdo A, et al. Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest. 2012;142:367–76.
18. Davidson AC, Banham S, Elliott M, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl. 2):ii1–35.

Noninvasive Ventilation Failure

35

Aslıhan Gürün Kaya, Aydın Çiledağ, and Akın Kaya

Abstract

Noninvasive ventilation (NIV) is widely used in patients with respiratory failure. The need for invasive mechanical ventilation or death during NIV therapy has been defined as NIV failure. Predictors of NIV failure has been determined. Early recognition of the findings of NIV failure is necessary to not delay the need for invasive mechanical ventilation.

Keywords

Noninvasive ventilation · Noninvasive ventilation failure · Noninvasive ventilation success · Respiratory failure

Abbreviations

APACHE	Acute Physiologic Assessment and Chronic Health Evaluation Score
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CPE	Cardiopulmonary edema
FiO_2	Fractional inspired oxygen
GCS	Glasgow Coma Scale
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation
$PaCO_2$	Partial arterial carbon dioxide pressure
PaO_2	Partial arterial oxygen pressure
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment
SpO_2	Oxygen saturation

A. Gürün Kaya (✉) · A. Çiledağ · A. Kaya
Ankara University Faculty of Medicine, Department of Chest Diseases, Ankara, Turkey
e-mail: agkaya@ankara.edu.tr

35.1 Introduction

Noninvasive ventilation (NIV) is widely used in patients with respiratory failure of different causes to avoid endotracheal intubation. But, the success of NIV application depends on the clinician's expertise, selection of patients, choice of interface, ventilator settings, and patient's compliance. The need for invasive mechanical ventilation or death during NIV therapy has been defined as NIV failure. NIV failure may occur after a few hours of ventilation or one or more days later [1, 2].

The established indications of NIV therapy are as follows: moderate to severe dyspnea, tachypnea, acute or acute on chronic ventilatory failure (pH < 7.35, partial arterial carbon dioxide pressure-$PaCO_2$ > 45 mmHg), signs of increased work of

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_35

breathing such as using accessory respiratory muscles, and moderate-severe hypoxemia where the ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) < 200 [1–3].

After determining the patient with the appropriate indication, patients should be evaluated in terms of contraindications for NIV applications. Cardiorespiratory arrest, severe hemodynamic instability, non-hypercapnic coma, multiple organ failure, inability to protect airway or clear secretions, and severe upper gastrointestinal bleeding are contraindications for NIV therapy [4, 5].

In some of the patients, NIV therapy fails because of disease progression or lack of adequate ventilation. It is not always clear which patients will benefit from NIV initially, but there are recognized predictors for NIV failure [3].

At the beginning and continuation of NIV therapy, clinicians should monitor patients closely and consider the predictors of NIV failure including the etiology of respiratory failure, level of consciousness, type of interfaces, parameters of ventilator settings, patient's tolerance and comfort, and respiratory parameters. Early recognition of the signs indicating NIV failure is critical to not delay the need for invasive mechanical ventilation (IMV) [3–5].

35.2 Discussion and Analysis of the Main Topic

35.2.1 Determinants of NIV Failure and Success

35.2.1.1 Etiology of Respiratory Failure

NIV applications have become the primary treatment modality in patients with cardiogenic pulmonary edema (CPE) and hypercapnic respiratory failure related to chronic obstructive pulmonary disease (COPD) exacerbation. It was shown that NIV reduced mortality and intubation rates were comparable with standard therapy in patients with acute decompensated respiratory failure complicating an acute exacerbation of COPD. CPE is the other clinical condition in which the benefits of NIV therapy have been well-recognized. Thus, the rate of NIV failure is very low in patients with CPE. Patients with other etiologies are less likely to benefit.

NIV is also used in hypoxemic respiratory failure in immunosuppression conditions and weaning from IMV in chronic hypercapnic patients. Although some studies showed the favorable outcomes of NIV treatment in patients with hypoxemic respiratory failure due to pneumonia, the usage of NIV is weakly recommended in these patient groups. NIV failure is more common in hypoxemic respiratory failure due to pneumonia or acute respiratory distress syndrome (ARDS). It is crucial to consider the etiology of hypoxemic respiratory failure (cardiogenic or noncardiogenic) and the severity of hypoxemia [1, 3, 6, 7].

35.2.1.2 The Severity of the Respiratory Failure

Oxygenation impairment, as shown by a decreased PaO_2/FiO_2, is one of the well-documented predictors of NIV failure. Previous data showed that PaO_2/FiO_2 ratios could predict NIV failure in patients with community-acquired pneumonia. Similarly, a low level of PaO_2/FiO_2 at admission was found to be a risk factor for NIV failure in immunocompromised patients with pneumonia. Several studies showed average PaO_2/FiO_2 < 150 at both baselines and after 1 h of NIV therapy predict NIV failure. Oxygen saturation measured by pulse oximetry (SpO_2) to a fraction of inspired oxygen (FiO_2) ratio (SpO_2/FiO_2) can also be used as a surrogate of PaO_2/FiO_2 in evaluating patients with hypoxemic respiratory failure [1–3].

The pH level of arterial blood gases is an indicator of the severity of hypercapnia and has been shown to be a factor in predicting NIV success. The low level of pH (pH < 7.25) at baseline is a risk factor for NIV failure. Furthermore, pH improvement one hour after the initiation of NIV therapy is shown to be a predictor of the success of NIV. Persistence of low pH after 1 h of NIV therapy is associated with an increased risk of NIV failure [3, 7, 8].

35.2.1.3 Mental Status

Altered mental status is an absolute or relative contraindication for NIV application. These patients are at risk for aspiration; in consequence of they could not protect their airway. Cognitive impairment may develop after the initiation of NIV therapy as well as at first. So, the monitoring of consciousness of the patients is required. The mental status of the patients can be evaluated with the Glasgow Coma Scale (GCS) or the Kelly–Matthay score. Recent data showed that low GCS score was associated with NIV failure. The Kelly–Matthay score was also evaluated in some studies, and a score of >3 may predict for depressed consciousness and high risk of NIV failure [7].

35.2.2 Severity of Disease

Previous studies suggested that baseline disease severity scores are associated with NIV therapy outcomes. Higher Sequential Organ Failure Assessment (SOFA), Acute Physiologic Assessment and Chronic Health Evaluation Score (APACHE II), and Simplified Acute Physiology Score (SAPS II) were found associated with NIV failure [3, 5, 8].

35.2.2.1 Poor Cough Reflex and Excessive Secretions

Cough is a mechanism that removes excessive secretions from airways. Weakness in cough reflex indicates a decreased ability to maintain airway patency and associate with aspiration risk. No/weak cough strength is found to be associated with NIV failure. Increased airway secretions are a characteristic of patients with pneumonia. If excessive secretions cannot be removed from the airway, atelectasis may occur, then gas exchange is diminished. This may explain the NIV failure in these patients. Patients with excessive respiratory secretions or without improvement after 60 min of NIV may also be at high risk of failure [1, 4, 9].

35.2.2.2 Respiratory Rate

Studies suggested that an average respiratory rate > 25 breaths/min on NIV is a predictor of failure. Respiratory rate is one of the indicators of increased work of breathing. An increased respiratory rate at the initiation of therapy and lack of reduction of respiratory rate after 1 hour of NIV therapy have been shown to be associated with NIV failure. Respiratory rate should be monitored every 30 min for the first 12 h and then hourly after the initiation of NIV therapy [3, 7].

35.2.2.3 NIV Tolerance

Tolerance to the noninvasive ventilation interface is another key for NIV success. The choice of the interface depends on the patient's characteristics, ventilation modes, and the type of respiratory failure. A suitable-sized mask should be selected based on the patients' facial type. When this balance between skin compression and excessive air leaks is not achieved, patient tolerance deteriorates, and treatment failure may occur. Claustrophobic reactions may be seen with an oronasal and full-face mask. Patient discomfort and mask intolerance are one of the major cause of NIV failure [4, 10].

35.2.2.4 Other Factors

Low BMI, increased white blood cell count, low serum potassium, and an increased heart rate are reported as risk factors for NIV failure. The experience of the clinicians is another critical component of NIV success. Also, the delay between admission and NIV use, duration of NIV use, and increase in radiographic infiltrates within the first 24 hours were shown as other risk factors for NIV failure [5, 6].

35.3 Conclusion Discussion

In conclusion, there are numerous risk factors for NIV failure. Every clinician should be aware of these risk factors and monitor each patient's course and response to NIV therapy. Early recognition of the findings of NIV failure is necessary to not delay the need for IMV.

Key Major Recommendations

- Noninvasive mechanical ventilation is widely used in patients with acute respiratory failure.
- NIV is not always successful, and in the case of NIV failure, a delay in intubation may cause increased morbidity and mortality.
- The selection of appropriate patients is significant for NIV success, and the predictors of NIV success or failure may help the selection of appropriate patients.
- Early recognition of the signs indicating NIV failure is very important to not delay the need for invasive mechanical ventilation (IMV).

References

1. Esquinas AM, Benhamou MO, Glossop AJ, Mina B. Noninvasive mechanical ventilation in acute ventilatory failure rationale and current applications. Sleep Med Clin. 2017;12:597.
2. Mas A, Masip J. Noninvasive ventilation in acute respiratory failure. Int J Chron Obstruct Pulmon Dis. 2014;9:837–52.
3. Ozyilmaz E, Ugurlu AO, Nava S. Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. BMC Pulm Med. 2014;14
4. Duan J, Han XL, Huang SC, Bai LF. Noninvasive ventilation for avoidance of reintubation in patients with various cough strength. Crit Care. 2016;20
5. Xu XP, Zhang XC, Hu SL, Xu JY, Xie JF, Liu SQ, et al. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017;45:E727–33.
6. Hess DR. Noninvasive Ventilation for Acute Respiratory Failure. Respir Care. 2013;58:950–69.
7. Ergan B, Nasilowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev. 2018;27
8. Ciledag A, Kaya A, Ercen Diken O, Onen ZP, Sen E, Demir N. The risk factors for late failure of noninvasive mechanical ventilation in acute hypercapnic respiratory failure. Tuberk Toraks. 2014;62:177–82.
9. Scala R, Pisani L. Noninvasive ventilation in acute respiratory failure: which recipe for success? Eur Respir Rev. 2018;27
10. Brill A-K. How to avoid interface problems in acute noninvasive ventilation. Breathe. 2014;10:230–42.

Pharmacological Treatments and Pulmonary Function Tests

36

Hadeer S. Harb, Haitham Saeed, Yasmin M. Madney, and Mohamed E. A. Abdelrahim

Abstract

Many pharmacological agents could be used during NIV to treat various conditions contributing to patient respiratory failure. Aerosols should normally be administered during breaks from NIV. If the patient is dependent on NIV, the aerosol generator should be placed proximal to the patient and synchronized with inspiratory airflow. Patients on NIV should be closely monitored for clinical parameters/pulmonary functions until stabilized.

Keywords

Aerosol · Oxygen · Monitoring · Optimization Weaning

Abbreviations

AAEs	Acute asthma exacerbations
ABG	Arterial blood gases
AECOPD	Acute exacerbation in chronic obstructive pulmonary disease
AHRF	Acute hypercapnic respiratory failure
AutoPEEP	Unintended positive end-expiratory pressure
BiPAP	Bilevel positive airway pressure
BTS/RCP	British Thoracic Society/Royal college of physicians.
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CWD	Chest wall disease
ECG	Electrocardiogram
EPAP	Expiratory positive airway pressure
FiO_2	Fractional inspired concentration of oxygen
FPD	Fine particle dose
FPF	Fine particle fraction
h	Hour
HDU	High dependency unit
IC	Inspiratory capacity
ICU	Intensive care unit
IMV	Invasive mechanical ventilation

Supplementary Information The online version of this chapter (https://doi.org/10.1007/978-3-030-76197-4_36) contains supplementary material, which is available to authorized users.

H. S. Harb · H. Saeed · Y. M. Madney
M. E. A. Abdelrahim (✉)
Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_36

IPAP	Inspiratory positive airway pressure
iPEEP	Intrinsic positive end-expiratory pressure
IV	Intra-venous
JN	Jet nebulizer
MAP	Mean airway pressure
MIP	Maximal inspiratory pressure
MMAD	Mass median aerodynamic diameter
MVV	Maximal voluntary ventilation
NIV	Noninvasive ventilation
NMD	Neuromuscular disease
O_2COB	Oxygen Cost of Breathing
OHS	Obesity hypoventilation syndrome
OI	Oxygenation index
P0.1	Airway occlusion pressure
PaO_2/FIO_2	Partial pressure of arterial oxygen/ Fractional inspired concentration of oxygen
pCO_2	Partial pressure of carbon dioxide
PEEP	positive end-expiratory pressure
PEF	Peak expiratory flow
PH	An indicator of the relative acidity or alkalinity of a solution
PS	Pressure support
PSV	Pressure support ventilation
PTP	Pressure time product
PVD	Patient-ventilator dyssynchrony
RR	Respiratory rate
SABAs	Short-acting beta-agonists
SAMAs	Short-acting muscarinic antagonists
SaO_2	Oxygen saturation
$TcpCO_2$	Transcutaneous partial pressure of carbon dioxide
Te	Expiratory time
Ti	Inspiratory time
TV	Tidal volume
VC	Vital capacity
VE	Exhaled volume/breath
VMN	Vibrating mesh nebulizer
WOB	Work of breathing

36.1 Introduction

NIV is intended in the treatment of various conditions including stable chronic obstructive pulmonary disease (COPD) patients treated with chronic NIV, acute exacerbations of COPD (AECOPD), and end-stage disease with respiratory failure in patients with cystic fibrosis (CF) in addition to all causes of acute hypercapnic respiratory failure (AHRF). NIV is rarely used in acute asthma exacerbations (AAEs) due to a lack of official guidelines or consistent data reinforcing its effectiveness. Therefore, NIV is sometimes implemented as a short-term attempt in AAEs, oriented on avoiding intubation or transfer to the intensive care unit (ICU) [1]. Many pharmacological agents could be used during NIV including aerosolized medications that could be delivered through either nebulizers or pMDIs. Multiple factors could affect the efficiency of aerosol therapy during NIV and that must be considered by physicians responsible for treatment planning and drug dosage choice to achieve higher rates of successful NIV therapy [2]. While the patient is treated, ventilator requirements change and ventilator settings should be reviewed regularly which necessitate close monitoring of patient clinical parameters and pulmonary functions to meet new patient criteria, assess wearability, or predict NIV failure as early as possible for intubation. Several parameters are available for monitoring patient respiratory effort during NIV [2, 3]. Before considering NIV failure, there are some technical issues to be applied first to optimize ventilation settings [4]. Once patient clinical parameters or pulmonary functions get normalized, a weaning plan for NIV could be started [5]. This chapter describes the pharmacological treatments during NIV and factors affecting their efficiency, monitoring plan, methods for optimizing ventilator settings, and possible weaning plans for NIV.

36.2 Discussion and Analysis of the Main Topics

36.2.1 Pharmacological Treatments During NIV

36.2.1.1 Aerosol Therapy with NIV

The use of aerosol therapy during NIV has demonstrated a great clinical benefit to ventilated patients if compared to systemic delivery due to lower doses targeting the lungs with minimal side effects of drugs [6].

36.2.1.1.1 Pharmacological Agents

Many pharmacological agents could be used during NIV to treat various conditions contributing to patient respiratory failure including corticosteroids, bronchodilators, prostanoids, antibiotics, surfactants, mucolytics, and concentrated saline solutions.

Inhalation therapy for stable COPD patients treated with chronic NIV is oriented on bronchodilators (both short- and long-acting beta-agonists and muscarinic antagonists) and nebulized antibiotic therapy (e.g., colistin, tobramycin, or gentamycin). However, short-acting beta-agonists (SABAs), e.g., albuterol, and/or short-acting muscarinic antagonists (SAMAs), e.g., ipratropium bromide, are medications frequently used in the treatment of AECOPD as a rescue medication [1].

In AAEs, NIV may be implemented as a short-term attempt to avoid intubation or transfer to ICU. Patients treated for AAE with albuterol administered with bilevel positive airway pressure (BiPAP) exhibited greater improvement in peak expiratory flow (PEF) values than patients treated only with albuterol administered through standard nebulization. During corticosteroid nebulization, superficial fluid processing reveals a significant increase in the in-vitro deposition of aerosol particles and enhanced the drug's bioavailability. Moreover, positive pressures administered during NIV reduce aerosol particle diameter and respiratory rate (RR) but increase tidal volume (TV) and drug delivery. Furthermore, slower RR increased expiratory time that promotes particle sedimentation and influence aerosol deposition patterns during exhalation. Pressure support (PS) and continuous positive airway pressure (CPAP) are highly effective in reducing work of breathing (WOB) in patients with bronchoconstriction, which leads to a decrease in demand for bronchodilator use and enhances the response to aerosol therapy [1].

Nebulization with concentrated saline solutions is often used in the treatment of COPD and CF with a large amount of dense sputum. Generally, 0.9% NaCl is used, especially in patients with a tendency for bronchoconstriction. It is rather recommended to start with 3.5% hypertonic saline and then proceed with more concentrated solutions, up to 7%. This method oriented on increasing sputum clearance is often ineffective in patients with CF. Protocols based on recombinant human deoxyribonuclease followed by hypertonic saline or nebulized antibiotics such as tobramycin are implemented with these patients. Antibiotics that are typically administered intravenously (IV) may be also administered through nebulization, often as maintenance therapy. Nebulization therapy in that case is followed by chest physiotherapy [7]. Moreover, PSV implemented with CF patients during chest physiotherapy prevented oxygen desaturation. It was found that the higher the PS, the more significant the increase in TV, the greater the decrease in RR, and the higher the peripheral pulmonary aerosol deposition with stable CF. Routine use of bronchodilators is not recommended for CF patients. Nebulization of antibiotics is a well-established treatment method in CF, in the treatment of post-lung transplant patients and severe COPD patients with bronchial Gram-negative colonization [7].

36.2.1.1.2 Factors Affecting the Efficiency of Aerosol Therapy During NIV

Numerous factors influence the efficiency of aerosol therapy in NIV-ventilated individuals: ventilator related factors, like ventilation mode, circuit conditions, and interface type. Ventilation modes have a great impact on aerosol delivery due to diverse pressure settings or airflow rates. Generally, the PS mode reduces both inspiratory

effort and RR and increases TV and minute ventilation, thus improving arterial blood gases (ABG) values. It also minimizes areas of atelectasis, thanks to positive end-expiratory pressure (PEEP), and prevents small airways from closing, which may result in more uniform drug deposition than controlled modes [1].

Circuit humidity has the disadvantage of increasing aerosol particle size, which results in increased impaction losses and decreased aerosol delivery if compared to a dry circuit. During NIV, the air is additionally humidified during passage through the nasal cavity to the lung (relative humidity of the lungs approximately 99.5%). Many factors influence air humidification within NIV circuit, including the use of external humidifier, air temperature, breathing pattern (through the mouth or nose), air leak, and gas flow rate. High airflow rates (high pressures) may increase nasal resistance and induce bronchial hyperresponsiveness. Airway resistance is inversely proportional to the beneficial effects of bronchodilators. Heliox, an 80/20 mixture of helium/oxygen, makes airflow more laminar due to lower gas density, which reduces WOB in AECOPD, therefore, improving tolerance of therapy. Heliox increases aerosol deposition in peripheral lung tissues, decreasing its deposition in the upper airways in healthy individuals, therefore, reducing drug deposition in both the endotracheal tube and the ventilator circuit. It could be attributed to its physical characteristics, high viscosity and low density (compared to oxygen), that facilitate laminar and less turbulent airflow, generating longer expiration time, allowing hyperinflation reduction, therefore, increasing IC. Furthermore, PEEP application during exercise helps to reduce pulmonary hyperinflation and prolong exercise [1].

The choice of the interface must depend on the patient's underlying condition and comfort. Oronasal masks should be chosen for first-line treatment with NIV. They facilitate the rapid improvement of ABG in a patient with AECOPD and are effective if breathing through an open mouth cannot be eliminated. They are also easily adjusted with head straps. They are the best choice in patients receiving ipratropium bromide through nebulization. However, full face masks or helmets are the interfaces of choice in patients with acute hypercapnic respiratory failure (AHRF) who are breathing through the open mouth and suffer from claustrophobia or facial skin injuries but they are not suitable for aerosol therapy during NIV due to high patient exposure to aerosols (leak into the patient's eyes). Full face masks could not be used with ipratropium bromide due to its irritancy to the eye. Moreover, it was reported that acute angle-closure results from its administration, which is of special importance in patients with glaucoma. Nasal masks may be used in the patients who do not tolerate oronasal, helmet, or full face masks. In those cases, NIV may be conducted together with nebulization throughout the standard mouthpiece because nasal masks significantly reduced pulmonary aerosol deposition if compared to mouthpiece-based inhalation. It could be attributed to high drug deposition in the nasal passage (significant extra-thoracic particle deposition) and high air leak through the open mouth. Moreover, during continuous nebulization, pulmonary drug deposition may be significantly decreased if a patient removes a mouthpiece from their mouth. Nasal masks are also ineffective in case of nares obstruction. Therefore, its use was limited to patients with large sputum volume expectoration [1].

Secondly, aerosol-generator-related factors, like aerodynamic characteristics of aerosol (MMAD, FPD, and FPF), device type and its location in the circuit, and leak port positioning. Targeting aerosol is a matter of its particle size and inhalation rate. Particles >5 μm are mainly deposited in the large conducting airways and oropharyngeal region by inertial impaction to be subsequently swallowed and contribute minimally, if has oral absorption, to the therapeutic response. Particles 0.5–5 μm are deposited by sedimentation in small airways and alveolar regions. However, particles below 0.5 μm, mainly deposited by diffusion, are not deposited and re-exhaled. An increase in the inspiratory flow will enhance deposition by inertial impaction in the upper airways as well as the oropharynx. Also, an increased inhalation volume will lead to an increase in the penetration of particles deeper

into the lung and thus enhance deposition into the alveolar region. Moreover, longer inspiratory time allows for better aerosol deposition. It was reported that NIV settings impact pulmonary deposition of aerosols; higher inspiratory positive airway pressure (IPAP) improves pulmonary deposition; however, higher expiratory positive airway pressure (EPAP) decreases medication delivery. It is indicated to adjust NIV settings in a way that increases bronchial drug deposition of aerosol rather than oro-pharyngeal deposition, decreasing inspiratory pressures and prolonging the inspiratory time for the duration of drug administration [1].

Patients on NIV are incapable of inhaling drugs through standard DPIs due to severely decreased inspiratory capacity (IC) resulting from poor inspiratory muscle strength, diaphragm reposition, and secondarily impaired inspiratory flow rates (<30 L/min). Aerosol therapy may be administered to a patient receiving NIV through pMDIs or nebulizers. Delivery efficacy of pMDI is greater than that of nebulizers due to lesser medication loss during expiration with pMDIs. Pulmonary deposition achieved with vibrating mesh nebulizer (VMN) exceeded this achieved through jet nebulizers (JN) but deposition of a smaller nominal dose of salbutamol delivered from pMDI was comparable to the deposition of bigger doses from both nebulizers. However, due to frequent difficulties in synchronizing inhalation and pMDI actuation, especially in elderly patients who have low mental-state scores, hand strength, and ideomotor dyspraxia, there is an increasing need to implement aerosol therapies that reduce the necessity of such actuation coordination in practice when chronic NIV is intended. Nebulizers are most commonly used with chronic NIV [1]. The aerosol generator type may contribute to a four-fold difference in the pulmonary deposition of the aerosolized medication; therefore, physicians responsible for treatment planning and drug dosage choice should be aware of the characteristics of available devices.

Nebulized drugs given concomitantly with NIV in stable patients produced less benefit than when given while patients were breathing spontaneously. Brief discontinuation of NIV for the administration of aerosols appears to be safe. Accordingly, aerosol therapy is probably better given during breaks in NIV. This may also facilitate coughing and the clearing of respiratory secretions. If discontinuing NIV results in patient distress, it should be continued and a nebulizer sited proximal to the patient interface [6].

The nebulizer location between the leak port and the patient interface increases medication delivery during NIV independently of the aerosol generator type and, therefore, results in the best clinical effects (Fig. 36.1). There were previous reports that the use of masks with leak ports reduces pulmonary deposition if compared to masks without such a port. The positioning of the leak port is significant as it affects medication loss to the environment during expiration. It was concluded that the nebulizer location between patient interface and the leak port during NIV may result in the delivery of approximately 25% of the nominal dose in case of high IPAP and low EPAP settings [1]. Moreover, positioning the nebulizer before the humidifier decreased the pulmonary deposition of aerosol during NIV in the pediatric lung model. Therefore, humidification during acute NIV is not routinely indicated. Also, it is essential to synchronize aerosol generation with inspiratory airflow of a ventilator. Intermittent operation of the nebulizer, synchronized with inspiratory airflow from the ventilator, is more efficient for aerosol delivery than a continuous aerosol generation. Similarly, the actuation of a pMDI must be synchronized with the precise onset of inspiratory airflow from the ventilator to minimize aerosol wastage during the exhalation phase of the breathing cycle [8].

Additionally, there are patient-related factors, like underlying diagnosis as an indication for NIV, breathing parameters, the severity of airway obstruction, tolerability of particular mask/interface type, synchronization of inspiration with intermittent drug flow, patient-ventilator synchrony, intrinsic positive end-expiratory pressure (iPEEP) presence, and excessive leakage that could affect the efficiency of aerosol therapy during NIV and must be considered by health care professionals to individualize NIV therapy [1].

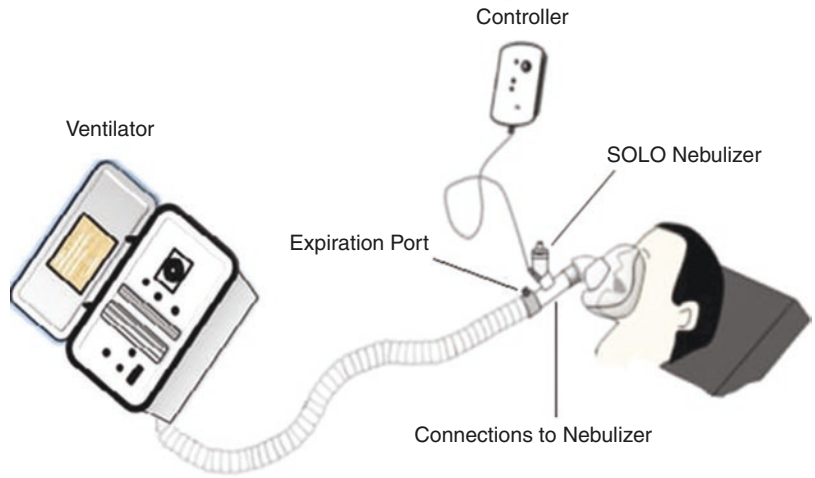

Fig. 36.1 Recommended nebulizer location within the NIV circuit

36.2.1.2 Supplemental Oxygen Therapy with NIV

Controlled oxygen therapy should be used in patients with AHRF due to CF, AECOPD, neuromuscular disease (NMD), chest wall disease (CWD), or obesity hypoventilation syndrome (OHS). Oxygen enrichment should be adjusted to achieve oxygen saturation (SaO_2) of 88–92% in all causes of AHRF treated by NIV. This is usually easily achieved in AECOPD, but severe hypoxemia may complicate AHRF in other diseases such as CWD [2].

Introducing oxygen directly into the NIV mask was more effective than oxygen introduced at the ventilator end of the tubing; so oxygen should be entrained as close to the patient as possible (at or near the mask). The flow rate of supplemental oxygen may need to be increased when ventilatory pressure is increased to maintain the same SaO_2 target but the higher the inspiratory pressure, the lower the additional benefit with higher flow rates above 4 L/min (because higher pressures increase leak and delay ventilator triggering). This promotes patient-ventilator dyssynchrony (PVD), which prompts a careful frequent check of SaO_2 [2]. Technically advanced NIV ventilators with an integral oxygen blender that allow precise oxygen blending (and a higher fractional inspired concentration of oxygen "FiO_2" enrichment) are better recommended when hypoxemia is severe and oxygen at 4 L/min fails to maintain $SaO_2 > 88\%$ [9].

36.2.1.3 Sedation with NIV

Patient agitation and distress are very common in AHRF and may be made worse by the application of NIV before gas exchange improvement and WOB reduction. Relieving patient distress is an important goal and might be expected to increase comfort and NIV success. However, sedatives, anxiolytics, and/or opiates are infrequently used due to the risk of depressing respiratory drive. Case series have reported that infusions of propofol, dexmedetomidine, remifentanyl, and midazolam are safe, improve patient comfort, and reduce the failure rate of NIV. Dexmedetomidine is notable for its ability to provide sedation without risk of respiratory depression (unlike propofol and fentanyl) and can provide cooperative or semi-rousable sedation. In another report, the addition of infused dexmedetomidine to a standard protocol of "as needed" bolus IV midazolam and fentanyl failed to show benefit, but sedation goals were readily achieved and there was good NIV tolerance and success with the standard protocol [2]. There is inadequate evidence to guide the use of sedation/anxiolysis in acute NIV. Opiates are more preferred than benzodiazepines because the latter promotes upper airway obstruction through inhibiting the pharyngeal dilating muscles. Their use in a critical care setting is reported to improve outcome and reduce patient distress [10]. They should only be used with close monitoring in a high dependency unit (HDU) or ICU setting. In

the agitated/distressed and/or tachypneic individual on NIV, IV morphine 2.5–5 mg (±benzodiazepine) may provide symptom relief and may improve tolerance of NIV [2].

36.2.2 Monitoring of Patients During NIV

The mechanical characteristics of the ventilated lung can only be interpreted when the volume of the lung, elastic properties, and degree of airway obstruction have been accurately quantified by pulmonary function measurements. Clinical parameters and pulmonary function measurements could provide useful diagnostic and therapeutic information to assess the weanability of the patient or guide in the selection of appropriate ventilator settings in the case of PVD. PVD may be caused by excessive mask leak, insufficient or excessive IPAP, the inappropriate setting of Ti or Te, high levels of iPEEP, or excessively sensitive triggers. Inappropriate use of NIV can lead to NIV failure and morbidity. Therefore close monitoring of clinical parameters including pulmonary functions during NIV is imperative to mitigate any potential injury and provide effective and safe ventilatory support with appropriate weaning at a reasonable time. All patients started on NIV should be monitored closely for signs of NIV failure until stabilized [11].

36.2.2.1 Monitoring of Clinical Findings During NIV

This should be used to formulate a management plan especially within the first 4 h of NIV assist to decide if there is a need to escalate to intubation or not. SaO_2 should be continuously monitored during NIV with intermittent measurement of the partial pressure of carbon dioxide (pCO_2), pH, and ABG measurement before and following starting NIV. Transcutaneous pCO_2 ($TcpCO_2$) monitoring is a commonly employed investigation in-home ventilation units and is increasingly being employed in hospitals. Also, RR and heart rate (HR) is necessary. ECG monitoring is advised if the patient has an HR >120 bpm or if there is dysrhythmia or possible cardiomyopathy [2]. The schedule for the monitoring plan of patient clinical parameters during the first 12 h of NIV is summarized in Table 36.1.

Table 36.1 Schedule for monitoring plan of patient clinical parameters during the first 12 h of NIV

Clinical parameter	Schedule
– ABG – RR – HR	– Baseline observations
– Pulse oximetry – Electrocardiogram[a]	– Continuous measurement during the first 12 h
Repeat ABG	– After 1 h of NIV therapy and 1 h after every subsequent change in settings – Further ABG at 4 h or earlier in patients who are not improving clinically
– RR – HR – Level of consciousness – Patient comfort – Compliance – Chest wall movement – Ventilator synchrony – Accessory muscle use – Mask fit (skin condition and degree of the leak)	Frequent clinical monitoring (acutely ill patients): – Every 15 min in the first hour – Every 30 min in the 1–4 h period – Hourly in the 4–12 h period

ABG arterial blood gas measurements, *RR* respiratory rate, *HR* heart rate, *ECG* electrocardiogram
[a]With existing cardiomyopathy

Some laboratory indices are more sensitive than clinical findings; an unimproved or worsened partial pressure of arterial oxygen/fractional inspired concentration of oxygen ratio (Pa_{O2}/FI_{O2}) during a 1 h NIV accurately predicts NIV failure. Moreover, the oxygenation index (OI) provides a superior estimate of lung function involvement and is a better predictor of NIV failure if compared with the Pa_{O2}/FI_{O2} ratio [12].

36.2.2.2 Monitoring of Pulmonary Functions During NIV

In critically ill patients, special constraints and problems are important to be considered by the therapist such as safety and patient ability to cooperate during pulmonary functions measurement [3]. Basic measurements such as maximal inspiratory pressure (MIP), vital capacity (VC),

TV, maximal voluntary ventilation (MVV), exhaled volume/breath (VE), and RR are commonly made to assess weanability. For the difficult-to-wean patient, WOB, pressure time product (PTP), airway occlusion pressure (P0.1), and oxygen cost of breathing (O_2COB) may be of potential value (lack evidence). Also, measurements of compliance, resistance, discomfort, air leaks, mean airway pressure (MAP), and unintended positive end-expiratory pressure (autoPEEP) provide useful diagnostic and therapeutic information. Finally, waveform monitoring can reveal patient-ventilator interactions such as autoPEEP, lung overdistension, patient effort, or the presence of secretions. Waveform monitoring can bring important issues to the close attention of the practitioners involved in the management of the ventilated patient [3].

36.2.3 Possible Outcomes of Patient Monitoring During NIV

The commonest reasons for NIV failure are excessive mask leak, insufficient PS, and PVD. Before considering NIV to have failed, always check that common technical issues have been addressed and ventilator settings are optimal.

36.2.3.1 Optimizing Ventilator Settings During NIV

While the patient recovers, ventilator requirements change, and ventilator settings should be reviewed regularly. Therefore, careful patient and display monitoring help to optimize ventilator settings. It could be achieved by optimizing ventilatory support (i.e., increasing PS, adding PEEP, increasing inspiratory flow trigger, and using low RR for the helmet) and checking factors for PVD (i.e., air leaks, water in the circuit, noise) and taken care of promptly. The leak should always be minimized by mask adjustment and/or by changing the mask type. Positional upper airway obstruction may result in ineffective NIV. It is often indicated by a variable mask leak. Care is needed to ensure head flexion is avoided, particularly in sleep (Table 36.2). As gas exchange will improve with increased alveolar ventilation, NIV settings should be optimized before increasing the FiO_2. If that is ineffective, or if this results in distress, a senior review is indicated while the FiO_2 is temporarily increased. Moreover, neurally adjusted ventilatory assist reduces PVD by reducing the triggering and cycling delays, especially at higher levels of assistance and, at the same time, preserves spontaneous breathing and blood gases [4]. Finally, patients who benefit from NIV during the first 4 h of treatment should receive NIV for as long as possible (minimum of 6 h) during the first 24 h and treatment should last until the acute cause has resolved, commonly about 2–3 days. However, the use of NIV should not delay escalation to invasive mechanical ventilation (IMV) if there is persistent acidosis (PH < 7.15) or deterioration of the case despite attempts to optimize the delivery of NIV. The

Table 36.2 Technical issues to optimize NIV delivery

Problem	Causes	Solutions
Ventilator cycling independently of patient effort	– Inspiratory trigger sensitivity is too high – Excessive mask leak	– Adjust trigger – Reduce mask leak
Ventilator not triggering despite visible patient effort	– Excessive mask leak – Inspiratory trigger sensitivity too low	– Reduce mask leak – Adjust trigger – For NM patients consider switch to PCV
Inadequate chest expansion despite apparent triggering	– Inadequate tidal volume	– Increase IPAP – In NMD or CWD consider longer Ti
Chest/abdominal paradox	– Upper airway obstruction	– Avoid neck flexion – Increase EPAP
Premature expiratory effort by patient	– Excessive Ti or IPAP	– Adjust as necessary

EPAP expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *NIV* noninvasive ventilation, *NMD* neuromuscular disease, *CWD* chest wall disease, *PCV* pressure-controlled ventilation, *Ti* inspiratory time

decision of IMV should normally be made within the first 4 h or sooner of starting NIV as improvements in RR, HR, and ABG parameters are usually apparent within this time. Moreover, IMV rather than further NIV should be considered in patients suffering "late failure" (defined as a failure after 48 h of NIV) [4].

36.2.3.2 Weaning from NIV

It is appropriate to start a weaning plan for NIV when there has been a normalization of pH and pCO_2 or a general improvement in the patient's condition as presented by arterial pH $\geq$ 7.35, SpO_2 > 90% on FiO_2 $\leq$ 50%, respiratory rate $\leq$ 25/min, heart rate $\leq$ 120/min, systolic blood pressure $\geq$ 90 mmHg, and no signs of respiratory distress like agitation, diaphoresis, or anxiety following the first 24 h or longer [5].

36.2.3.2.1 Stepwise Reduction of the Duration of NIV Use

This strategy involves gradually increasing the NIV free interval over a few days (usually 2–3 days) and then complete the removal of NIV (Fig. 36.2). BTS/RCP recommends a protocol which takes 4 days for weaning. In this protocol, patients continue NIV for as much as possible on day 1, for 16 h (including 6 h–8 h overnight) on the day 2 h and 12 h on the day—3 (including 6 h–8 h overnight). NIV may be discontinued on day 4 unless continuation is clinically indicated [5].

36.2.3.2.2 Stepwise Reduction in Pressure Support

It involves gradual reduction (2–4 cm of H_2O) of IPAP and EPAP every 4 h–6 h. The NIV may be removed once the patient can tolerate the IPAP of 6–8 cm of H_2O and EPAP of 4–6 cm of H_2O [5].

36.2.3.2.3 Immediate Withdrawal of NIV

This strategy involves the immediate removal of NIV once the patient is fulfilling above mentioned weaning criteria. It has the highest failure rate leading to the re-institution of NIV, so it is not favored by clinicians [5].

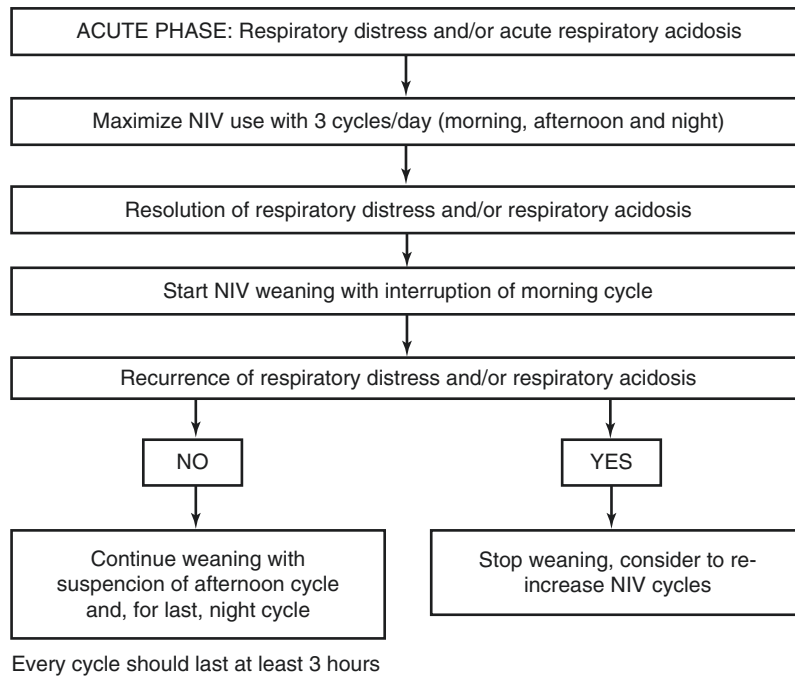

Fig. 36.2 Stepwise reduction of the duration of NIV use

36.3 Conclusion Discussion

In conclusion, once NIV is started, patients should be closely monitored until adequately stabilized, paying attention not only to vital signs and gas exchange but also to compliance, resistance, discomfort, air leaks, patient-ventilator interaction, and pulmonary functions. The proper pharmacological treatment, proper choice of interface and aerosol generator, proper positioning within the circuit, optimizing ventilatory support with patient ventilatory requirements, and accurate clinical/instrumental monitoring of PVD are crucial to minimizing the risk of NIV failure.

Key Major Recommendations

- Nebulized drugs should normally be administered during breaks from NIV. If the patient is dependent on NIV, nebulized drugs can be given via a nebulizer inserted into the ventilator circuit, proximal to the patient interface. Intermittent operation of the nebulizer should be synchronized with inspiratory airflow. Similarly, the actuation of a pMDI must be synchronized with the precise onset of inspiratory airflow from the ventilator.
- The flow rate of supplemental oxygen may need to be increased when ventilatory pressure is increased to maintain the same SaO_2 target. At flow rates >4 L/min, promptly a careful check for PVD should be done. A ventilator with an integral oxygen blender is recommended if oxygen at 4 L/min fails to maintain $SaO_2 > 88\%$.
- In the agitated/distressed and/or tachypneic individual on NIV, IV morphine 2.5–5 mg (±benzodiazepine) may provide symptom relief and may improve tolerance of NIV, only administered in HDU or ICU.
- All patients started on NIV should be monitored closely for SaO_2, pCO_2, pH, ABG, RR, HR, and ECG monitoring (for possible cardiomyopathy) besides waveform monitoring until adequately stabilized besides measurements of compliance, resistance, discomfort, air leaks, MAP, and autoPEEP. Basic measurements such as MIP, VC, TV, MVV, VE, and RR are commonly made to assess weanability.
- Before considering NIV to have failed, NIV settings should be optimized by optimizing ventilatory support (increasing PS, adding PEEP, increasing inspiratory flow trigger, and using low respiratory rates for the helmet) and checking factors for PVD (air leaks, water in the circuit, noise) and taken care of promptly (preferring neurally adjusted ventilatory assist). If that is ineffective then FiO_2 should be increased.

References

1. Rzepka-Wrona P, et al. Inhalation techniques used in patients with respiratory failure treated with noninvasive mechanical ventilation. Can Respir J. 2018;
2. Davidson AC, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl. 2):ii1–ii35.
3. Adams A. Pulmonary function in the mechanically ventilated patient. Respir Care Clin N Am. 1997;3(2):309–31.
4. Spahija J, et al. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med. 2010;38(2):518–26.
5. Hadda V, Kumari R. Protocols for weaning from NIV: appraisal of evidence. Insights Chest Dis. 2016;1:14.
6. Mukhopadhyay A, et al. Effects of inhalational bronchodilator treatment during noninvasive ventilation in severe chronic obstructive pulmonary disease exacerbations. J Crit Care. 2009;24(3):474.e1–5.
7. Elkins MR, Bye PT. Inhaled hypertonic saline as a therapy for cystic fibrosis. Curr Opin Pulm Med. 2006;12(6):445–52.
8. Miller DD, et al. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. Am J Respir Crit Care Med. 2003;168(10):1205–9.
9. Kaul S, et al. The effect of entrainment site and inspiratory pressure on the delivery of oxygen therapy during non-invasive mechanical ventilation (NIMV) in acute COPD patients. Eur Respir Rev. 2006;15(101):190–1.
10. Longrois D, et al. Sedation in non-invasive ventilation: do we know what to do (and why)? Multidiscip Respir Med. 2014;9(1):56.
11. Bertoni M, Spadaro S, Goligher EC. Monitoring patient respiratory effort during mechanical ventilation: lung and diaphragm-protective ventilation. In: Vincent J-L, editor. Annual update in intensive care and emergency medicine. Cham: Springer International Publishing; 2020. p. 21–35.
12. Carron M, et al. Predictors of failure of noninvasive ventilation in patients with severe community-acquired pneumonia. J Crit Care. 2010;25(3):540.e9-540. e14

Part V

Are There Any Implications of Lung Function Measurement and Health Care Organization in Noninvasive Ventilation?

37

Pulmonary Function Tests in Hospitalized Patients/Setting (Specialized Respiratory Care, High Dependency/Intensive Care Unit)

Sara Dias, Bruno Cabrita, Ana Luísa Fernandes, and Márcia Araújo

Abstract

Noninvasive ventilation (NIV) is widely used during chronic or acute respiratory failure. However, a successful response to NIV will depend on adequate monitoring, as the delay in recognition of unresponsiveness to NIV may be harmful and devastating for the patient. In this chapter, we focus on the different monitoring techniques available in the hospital setting.

Keywords

Noninvasive ventilation · Intensive care unit · Diaphragm · Respiratory muscle · Monitoring

Abbreviations

ABG	Arterial blood gas
ARF	Acute respiratory failure
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
DD	Diaphragmatic dysfunction
EMG	Electromyography
HRF	Hypercapnic respiratory failure
ICS	Intensive Care Society
ICU	Intensive care unit
NIV	Noninvasive ventilation
$PaCO_2$	Arterial CO_2 pressure
PCO_2	Partial pressure CO_2
Pdi	Transdiaphragmatic pressure
Pes	Esophageal pressure
$PetCO_2$	End-tidal pressure CO_2
PNS	Phrenic nerve stimulation
PNSmg	Magnetic stimulation phrenic nerve stimulation
PNStc	Transcutaneous electrical phrenic nerve stimulation
$PtcCO_2$	Transcutaneous pressure CO_2
PTPdi	Diaphragmatic pressure-time product
RHDU	Respiratory high dependency unit
SpO_2	Pulse oximetry
TF	Thickening fraction

37.1 Introduction

A hospitalized patient under noninvasive ventilation (NIV) is usually treated in one of these three levels of facilities: intensive care unit (ICU), a respiratory high dependency unit with expertise in NIV (RHDU), or the respiratory general ward. Important factors to consider include the patient's need for monitoring, the unit's competences, the skills, and experience of the unit staff. The sever-

S. Dias (✉) · B. Cabrita · A. L. Fernandes
M. Araújo
Pulmonology Department at Hospital Pedro Hispano, Matosinhos, Portugal

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_37

ity of the patient's respiratory compromise and risk of NIV failure determine the intensity of monitoring needed [1].

ICU should be recommended as a location for NIV treatment only for severely ill patients, with a high risk of NIV failure, such as severe respiratory acidosis (pH <7.20–7.25), significantly impaired level of consciousness, and multi-organ failure, but the decision about admission to ICU should be based on other multiple parameters [1].

The ICU setting provides some advantages over the RHDU: high levels of nurse staffing, facilities for prompt escalation of therapy, and access to invasive or highly specialized monitoring, such as pulmonary artery catheterization and determination of central venous oxygen saturation, invasive arterial blood pressure, and transdiaphragmatic pressure [1]. On the other hand, different RHDUs offer variable levels of care, but usually they are all composed of staff experienced in NIV. On a RHDU, vital parameters are continuously monitored with noninvasive methods to early detection of NIV's failure [1].

Despite countless studies on this topic, no evidence-based data seems to prove the best way of monitoring NIV neither trials comparing different levels of monitoring, because this is not an issue that could be clearly standardized. Usually, the level of monitoring is dependent on the risk of NIV failure: the more risk factors present, the higher the level of monitoring needed [1].

37.2 Discussion and Analysis of the Main Topics

Several clinical parameters such as patient comfort, tolerance of the interface, accessory muscle use, respiratory and heart rates, blood pressure, and oxygenation should be monitored every 30 min for the first hours of NIV and regularly thereafter [1, 2]. Additionally, the consciousness and patient's ability to protect upper airways with an effective cough should be monitored on a routine basis as well as the screening of delirium during NIV [1].

Besides basic parameters monitored during NIV, as in the case of gas exchange monitoring, there are countless other parameters, according to the levels of intensity of care and monitoring necessary.

37.2.1 Monitoring of Gas Exchange

According to the British Thoracic Society (BTS)/Intensive Care Society (ICS) guidelines, oxygen saturation should be monitored continuously and arterial CO_2 pressure ($PaCO_2$) and pH should be monitored intermittently [3].

37.2.2 Pulse Oximetry

The target of arterial oxygen saturation measured by pulse oximetry (SpO_2) under NIV should be different in hypercapnic and hypoxemic patients. Oxygen enrichment should be adjusted to achieve SaO_2 88–92% in all causes of acute hypercapnic respiratory failure (HRF) treated with NIV. However, before increasing the fractional inspired concentration of oxygen, NIV settings should be optimized as this may lead to an increase in alveolar ventilation and, therefore, an improvement in gas exchange [3].

Pulse oximetry has become a standard monitoring device and therapeutic interventions are frequently based on SpO_2 values, although its accuracy is apparently influenced by the type of oximeter, the presence of hypoxemia, and the patient's hemodynamic status [1].

37.2.3 Arterial Blood Gas Analysis

Arterial blood gas (ABG) analysis is the gold standard for monitoring respiratory failure. After the first trial of ventilation, pH and arterial oxygen pressure/inspiratory oxygen fraction ratio changes have important prognostic value in hypercapnic and hypoxemic acute respiratory failure (ARF) patients, respectively. Furthermore, the advantages of ABG measurements include the assessment of additional parameters such as hemoglobin and electrolytes [1].

Additionally, monitoring the partial pressure CO_2 (PCO_2) is essential to assess alveolar ven-

tilation in patients with chronic hypercapnic respiratory failure, particularly in those receiving nocturnal NIV. Measurement of arterial PCO_2, with an ABG analysis, for example, is recommended in these patients [4]. Typically, blood samples are taken either via a single arterial puncture or an arterial catheter [1]. However, these are painful methods and disrupt patient's sleep. Besides, it represents an isolated measurement and it may not be representative of varying status of alveolar ventilation during sleep [4]. Arterialized earlobe blood gas analysis is a simpler and less painful alternative to ABG. One advantage of RHDU/ICU is the possibility to use of an indwelling arterial line for blood sampling [3].

ABG measurements should be undertaken at baseline and 1–2 h after NIV. A positive response to NIV could be considered a decrease of 3 mmHg of PCO_2 and an increase of 0.03 in pH. Typically, ABG monitoring should be maintained until normalization of pH and arterial PCO_2 is achieved. After discontinuation of NIV, ABG should be repeated in cases of suspected relapse [1].

37.2.4 Transcutaneous CO_2

As mentioned above, measurement of arterial PCO_2 remains the gold standard to evaluate alveolar ventilation in patients receiving NIV, but it is preferable to monitor PCO_2 with a noninvasive and continuous method, for example, end-tidal ($PetCO_2$) and transcutaneous CO_2 ($PtcCO_2$), instead of ABG analysis.

According to Sanders et al. neither $PetCO_2$ nor $PtcCO_2$ monitoring provided an accurate reflection of $PaCO_2$ during sleep [5]. However, $PtcCO_2$ monitoring is independent of both air leakage and the underlying lung disease, and it seems to be more reliable than $PetCO_2$ [4].

An important limitation of $PtcCO_2$ monitoring is the possibility of technical drifts, which may have an impact, especially when monitoring is performed for a period of several hours or throughout the night. Store et al. showed that calibration drifts in $PtcCO_2$ values and the differences between transcutaneous and $PaCO_2$ have been low when modern monitors are used to assess $PtcCO_2$ and proved that overnight $PtcCO_2$ monitoring is a reliable and robust tool for assessing alveolar ventilation during sleep, suggesting that $PtcCO_2$ monitoring may become the new gold standard for nocturnal monitoring of alveolar ventilation in chronic HRF patients with positive pressure NIV [4].

According to BTS/ICS guidelines, $PtcCO_2$ measurement may better facilitate the discontinuation of NIV than measurement with arterial or capillary sampling. Thus, transcutaneous CO_2 monitoring could replace frequent ABG measurements for monitoring patients with ARF undergoing NIV, since it is reliable and more comfortable for the patient [3]. Although the evidence is growing about $PtcCO_2$ monitoring, the gold standard remains the $PaCO_2$ value. Besides, acidosis level can only be assessed accurately with ABG analysis [1].

37.2.5 End-Tidal CO_2

The measurement of $PetCO_2$ or capnography is used more frequently for intubated patients and it is not as accurate as $PtcCO_2$ due to the physiological dead space [1]. Furthermore, it is known to have limitations in parenchymal lung disease and in the case of air leakage around the mask or through the mouth, which regularly occurs with NIV [4].

Considering chronic obstructive pulmonary disease (COPD) patients, flow limitation, with the consequent incomplete emptying of the lung, and poor ventilation/perfusion ratios are possible arguments for the underestimation of $PaCO_2$ observed in invasively and noninvasively ventilated patients [1].

As shown by Sanders et al., $PetCO_2$ measured from exhaled gas in a mask does not provide a reasonable reflection of arterial values, particularly during the administration of supplemental oxygen or during positive pressure therapy via mask, which uses a delivery system that mandates constant flow through the mask or may be subject to unintentional leakage [5]. Therefore,

$PtcCO_2$ appears more appropriate for the continuous monitoring of $PaCO_2$ in NIV.

37.2.6 Monitoring of Cardiac Function

Besides improving the ventilatory system, NIV will also interfere with the cardiovascular system. For example, positive pressures may decrease arterial PCO_2 and simultaneously decrease cardiac output and oxygen delivery to tissues, mainly because it produces positive intrathoracic pressure throughout the respiratory cycle [1]. So cardiovascular function should be assessed continuously or periodically.

Blood pressure should be systematically assessed, and hypotension (systolic blood pressure < 90 mmHg) may be considered a relative contraindication to NIV. However, the impact of NIV on blood pressure is less significant than that of invasive ventilation [1].

In BTS/ICS guidelines, ECG monitoring is advised for all patients with a tachycardia above 120 beats per minute, dysrhythmia or known cardiomyopathy [3].

In some cases, echocardiography may be indicated to exclude acute pulmonary edema [3]. However, the technical quality of the echocardiographic visualization can be significantly limited due to conditions frequently present in this type of patients, for instance, emphysema, obesity or kyphoscoliosis [1].

37.2.7 Assessment of Respiratory Muscles and Diaphragm Functions

37.2.7.1 Lung Volumes

Few studies have been conducted in critically ill patients to examine the usefulness of lung volume measurements and, due to technical difficulties involved in these type of measurements, they are usually primarily evaluated in research institutions [6, 7]. Nevertheless, knowledge of functional residual capacity is essential if mechanical ventilation is considered and other lung function parameters, for example, the compliance of the respiratory system, are to some extent volume-dependent [7].

Lung volumes are classically measured by body plethysmography, which may be difficult and unsafe to use in critically ill patients [7].

Inductive plethysmography, through the determination of thoracoabdominal movements, indirectly measures respiratory muscle function and it seems to be an accurate noninvasive method of measuring tidal volume. However, it is difficult to calibrate and chest wall motion may reflect other events instead of respiratory muscle function, making it difficult to interpret and rely on in the ICU scenario [6].

37.2.7.2 Maximal Inspiratory and Expiratory Pressures

Respiratory muscle weakness may contribute to or worsen respiratory failure in critically ill patients. The ability to assess respiratory muscle strength and, therefore, risk of fatigue may enable the clinician to predict both the need for mechanical ventilation and the success of weaning. Maximal inspiratory and expiratory pressures can be measured directly in intubated patients, but with NIV it can be measured during a brief disconnection using a handheld pressure monitoring device. These maneuvers require a considerable degree of patient cooperation and coordination. Therefore, high values exclude clinically significant weakness, but low values are common and may reflect poor technique or effort as well [6, 8].

37.2.7.3 Esophageal and Transdiaphragmatic Pressure

Transdiaphragmatic pressure (Pdi), a specific measure of diaphragm muscle strength, is the difference between abdominal and pleural pressure. In practice, it is calculated by the difference between gastric and esophageal (Pes) pressures, measured by using air-filled or liquid-filled balloons attached to a nasogastric tube connected to a pressure transducer. Voluntary measurements of maximum Pdi can be obtained by having the patients inspire as forcefully as possible against a

closed airway or by having the patient sniff forcefully. This last one is more reproducible than the maximum inspiratory Pdi [8]. However, these procedures require the subject's cooperation and increase of Pdi may fail because of a lack of coordination, in the absence of any diaphragmatic abnormality [6].

According to clinical trials, prolonged Pes measurement seems to be feasible in ICU patients. Monitoring Pes can be used to track and even quantify the activity of the inspiratory and expiratory muscles and detect patient-ventilator asynchrony. However, analysis of work of breathing and energy expenditure are sophisticated parameters, the interpretation of which is complex and not suitable for routine monitoring [9]. Besides, gastric and esophageal balloons are not used routinely in clinical care, probably because of their invasiveness, even though they are extensively used for research purposes [8].

37.2.7.4 Diaphragm and Accessory Muscle Electromyography

Electromyography (EMG) comprises the temporal and spatial summation of neural impulses from the brain that are translated into muscle fiber action potentials. Diaphragm EMG can be acquired with surface or esophageal electrodes. The latter is more reliable mostly because of reduced cross talk from other muscles. Besides, its utility for research purposes, the EMG signal, referred to as the amplitude of the electrical activity of the diaphragm, can be obtained rather easily and continuously in ICU patients, which opens an opportunity for its use in patient monitoring. It may allow monitoring of respiratory muscle loading, patient-ventilator synchrony, and efficiency of breathing in critically ill patients [8, 9].

Alternatively, surface EMG can be used to detect the electrical activity of the diaphragm and other respiratory muscles. Practical aspects including a cross talk from other muscles, low signal-to-noise ratio in certain patients, because of obesity or edema, and impaired patient mobilization, limit routinely use of surface EMG in clinical practice [9].

37.2.7.5 Phrenic Nerve Stimulation

The diaphragm is innervated exclusively by the phrenic nerve, and thus phrenic nerve stimulation (PNS) provides a specific means to investigate the diaphragm independent of other inspiratory muscles and without the influence of the central nervous system [6]. PNS allows nonvoluntary evaluation of diaphragm strength, measured as the magnitude of twitch transdiaphragmatic pressure or twitch airway pressure. It is possible to evaluate the integrity of the phrenic nerve through the calculation of its conduction time and subsequent detection of phrenic nerve injury. Despite the extensive use of phrenic nerve stimulation in research settings, this technique is not applicable routinely for bedside monitoring because it is an invasive and, possibly, not a well-tolerated procedure [8].

Four main PNS techniques have been used: needle stimulation and implanted wire stimulation, both invasive and with the risk of hematoma and phrenic nerve damage, transcutaneous electrical PNS (PNStc), and magnetic stimulation (PNSmg). These last two techniques have been more extensively studied and have minimal side effects [6].

During PNStc, an externally applied electrical field induces depolarization of phrenic nerve fibers and, if the stimulus is intense enough, all fibers are activated synchronously, giving predictable and reproducible results representative of diaphragm properties alone. However, it may be uncomfortable for the patient when supramaximal stimulation is achieved, and it requires technical expertise that may be a source of variability [6].

Magnetic stimulation creates intense and brief magnetic fields, which, unlike electric currents, are only mildly attenuated by natural barriers such as skin and bone and can therefore reach deep nervous structures. The mechanisms of neural response to magnetic stimulation are different from those of the response to electrical stimulation, so the results obtained with the two techniques may have different interpretations. Magnetic stimulation applied to the cervical spine elicits a bilateral diaphragm contraction, as well as it stimulates other elements of the cer-

vical roots and nearby nerves, thus causing some contraction of the neck and upper rib cage muscles. PNSmg has the advantage of being relatively painless and is thus easily applicable in the clinical setting, with reliable results, although it lacks the specificity of PNStc for the diaphragm [6].

37.2.7.6 Lung Ultrasonography

Ultrasound has become a very popular option in the management of critically ill patients because of its portability, low cost, and the absence of contraindications. It is a noninvasive and radiation-free procedure, which can be performed quickly at the bedside in all patients, and enables a dynamic assessment of lungs, diaphragm, and pleura, which may give important clues for the management of patients requiring ventilation [1].

Bedside lung ultrasonography may diagnose some thoracic disorders and help to identify some causes of ARF. Lichtenstein et al. proposed an algorithm, the bedside lung ultrasound in emergency—the BLUE protocol. They compared lung ultrasonography results on initial presentation, performed on patients admitted on the ICU with ARF, with the final diagnosis. Three items on ultrasound were assessed: artifacts (horizontal A lines or vertical B lines), lung sliding, and alveolar consolidation and/or pleural effusion, combined with venous ultrasound analysis. These items were grouped to compose ultrasound profiles that would correspond to asthma or COPD (predominant A lines plus lung sliding), pulmonary edema (multiple anterior diffuse B lines with lung sliding), pulmonary embolism (normal anterior profile plus deep venous thrombosis), pneumothorax (anterior absent lung sliding plus A lines plus lung point), or pneumonia (anterior alveolar consolidations, anterior diffuse B lines with abolished lung sliding, anterior asymmetric interstitial patterns, posterior consolidations or effusions without anterior diffuse B lines) [10].

The work of breathing is a central physiologic parameter in the assessment of a critically ill patient's respiratory function. The diaphragm is the main respiratory muscle and plays a central role in the pathophysiology of respiratory failure. During the ultrasonographic evaluation of the diaphragm, there are two important parameters: measurement of diaphragmatic movement, defined as diaphragmatic excursion, and measurement of diaphragm thickness during end-expiration [1].

Vivier et al. evaluated the usefulness of diaphragm thickening to assess work of breathing in ICU patients and found a parallel decrease in diaphragmatic pressure–time product (PTPdi) and thickening fraction (TF) during NIV with increasing pressure support level, with a good correlation between the two parameters. PTPdi is the integration of the area under the transdiaphragmatic pressure curve versus time and is a very useful tool for quantifying respiratory muscle effort in mechanically ventilated patients and assess the oxygen cost of breathing, although its execution requires considerable attention. TF was obtained by calculating the difference between diaphragm thickness at end-inspiration and at end-expiration, with good repeatability of TF assessment for both intra-observer and inter-observer reproducibility [11].

Diaphragmatic dysfunction (DD) assessed by ultrasound is defined by Marchioni et al. as a change in diaphragm thickness <20% during tidal volume. They proved that DD was associated with a higher risk for NIV failure in patients with acute exacerbation of COPD, which was also reflected in higher mortality rates, longer mechanical ventilation duration, higher tracheostomy rate, and longer ICU stay. They also showed better accuracy of DD to predict NIV failure than baseline pH value and early change in both arterial blood pH and PCO_2 following NIV start [12].

37.2.7.7 Sleep Studies

NIV may induce sleep disruption due to interface intolerance and patient-ventilator asynchrony. On the other hand, NIV may improve sleep quality by decreasing the work of breathing and obstructive sleep apnea.

The acute setting is not an optimal timing for assessment of sleep, but Roche et al. performed an interesting study assessing sleep disturbances with a polysomnography 2–4 days after starting NIV for hypercapnic ARF. The authors found that sleep disturbances, such as abnormal electro-

encephalographic patterns, greater circadian sleep-cycle disruption and less rapid eye movement sleep, were associated with late NIV failure. The practical significance of this finding is unclear; however, this observation broadens the spectrum of the possibility of monitoring patients under NIV [13].

Despite the results of this study, it seems that sleep studies could be helpful, mostly in the recovery phase of ARF, especially for the detection of breathing-related sleep disorders and making decisions about chronic treatment. Besides, the analysis of the memory of a ventilator with adequate software can be very useful to analyze overnight ventilation and its efficacy [1].

37.3 Conclusion Discussion

NIV may be a lifesaving therapeutic option, useful either on chronic HRF or ARF. However, the benefits of NIV can be obtained only if adequate monitoring of patients is undertaken, which will depend on the severity of respiratory failure and the patient's general condition. Monitoring gas exchange is a basic parameter to monitor when a patient is treated with NIV, such as continuous monitoring of SpO_2 and periodic ABG analysis, but other sophisticated parameters may improve ventilation efficacy through assessment of respiratory muscles, diaphragm functions, and sleep quality.

Key Major Recommendations

- A hospitalized patient under NIV is usually treated in one of these three levels of facilities, according to the risk of NIV failure: ICU, a RHDU with expertise in NIV, or the respiratory general ward.
- Oxygen saturation should be monitored continuously, and $PaCO_2$ and pH should be monitored intermittently; noninvasive and continuous methods, for example, $PetCO_2$ and $PtcCO_2$, may be an alternative to ABG analysis.
- There are several techniques to evaluate respiratory muscle and diaphragm functions, but the most promising in clinical practice are transdiaphragmatic pressure, electromyography, and phrenic nerve stimulation.
- Ultrasonography is widely used in critically ill patients, and it enables a dynamic assessment of lungs, diaphragm, and pleura.

References

1. Ergan B, Nasilowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev. 2018;27
2. Practical Application of Noninvasive Ventilation in the Hospital Setting: A Supplement to the ERS/ATS Clinical Practice Guidelines for Noninvasive Ventilation for Acute Respiratory Failure, pp. 1–44.
3. Davidson C, Banham S, Elliott M, et al. BTS/ICS Guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71
4. Storre JH, Magnet FS, Dreher M, et al. Transcutaneous monitoring as a replacement for arterial PCO_2 monitoring during nocturnal non-invasive ventilation. Respir Med. 2011;105:143–50.
5. Sanders MH, Kern NB, Costantino JP, et al. Accuracy of end-tidal and transcutaneous PCO_2 monitoring during sleep. Chest. 1994;106:472–83.
6. Gibson GJ, et al. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166:518–624.
7. Numa AH, Newth CJL. Assessment of lung function in the intensive care unit. Pediatr Pulmonol. 1995;19:118–28.
8. Doorduin J, Van Hees HWH, Van Der Hoeven JG, Heunks LMA. Monitoring of the respiratory muscles in the critically Ill. Am J Respir Crit Care Med. 2013;187:20–7.
9. Heunks LMA, Doorduin J, Van Der Hoeven JG. Monitoring and preventing diaphragm injury. Curr Opin Crit Care. 2015;21:34–41.
10. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure the BLUE protocol. Chest. 2008;134:117–25.
11. Vivier E, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med. 2012;38:796–803.
12. Marchioni A, et al. Ultrasound-assessed diaphragmatic impairment is a predictor of outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease undergoing noninvasive ventilation. Crit Care. 2018;22:1–9.
13. Campo FR, et al. Poor sleep quality is associated with late noninvasive ventilation failure in patients with acute hypercapnic respiratory failure. Crit Care Med. 2010;38:477–85.

Discharge from Hospital to Home Care

38

Hilmi Demirkiran and Hafize Oksuz

Abstract

The care levels, locations, and transfers of patients during discharge are critical processes. Out-of-hospital discharge with ventilation support is associated with high mortality. Among the factors determining the success of HMV, the indication for HMV, current stage of disorder, comorbid conditions, likely progression of the disorder, and the level of dependency on ventilator support can be counted.

Keywords

Noninvasive ventilation · Pulmonary function
Readmission · Hospital discharge

Abbreviations

AHRF	Acute hypoxemic respiratory failure
ALS	Amyotrophic lateral sclerosis
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
DTF	Diaphragm thickening fraction
DU	Diaphragm ultrasonography
FEV	Forced expiratory volume
FVC	Forced vital capacity
HMV	Home mechanical ventilation
LU	Lung ultrasonography
MIE	Mechanical insufflation-exsufflation
MRC	Medical Research Council
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
REM	Rapid eye movement
VC	Vital capacity

H. Demirkiran (✉)
Department of Anesthesiology and Reanimation, Faculty of Medicine, Van Yuzuncu Yil University, Van, Turkey

H. Oksuz
Department of Anesthesiology and Reanimation, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey

38.1 Introduction

Home mechanical ventilation (HMV) can be used successfully for patients with chronic respiratory failure, especially chronic obstructive pulmonary disease (COPD)/emphysema, restrictive chest wall disorders, neuromuscular disease, and obesity hypoventilation syndrome. The estimated prevalence of HMV in Europe for 2005 is 6.6 per 100,000 people [1]. In the last decades, the number of patients who are dependent on ventilators after staying in the acute intensive care unit has gradually increased [2]. These patients are now discharged home from acute intensive care units. These patients have high comorbidity and limita-

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_38

tions of various organ functions. COPD patients treated with NIV for acute hypoxemic respiratory failure (AHRF) were found to have a high risk of recurrent AHRF in the following year. Chu et al. analyzed against potential risk factors the rehospitalization, recurrent AHRF, and death times of COPD patients with AHRF who survived after NIV treatment. One year after discharge, of those, 79.9% were rehospitalized, 63.3% had another life-threatening event, and 49.1% died. The survivors have spent a median of 12% of the following year in the hospital. Home oxygen use ($p = 0.002$) and APACHE II score ($p = 0.006$) predicted early recurrent AHRF or death; *Medical Research Council* (MRC) dyspnea score ($p < 0.001$) predicted premature death [3].

There is no guideline defining the criteria for patients being discharged from acute intensive care; however, typically patients who do not require intensive monitoring or who are considered by clinicians to be at low risk for physiological decompensation are housed on general care floors. Most unplanned intubation occurs in patients at risk of respiratory failure. However, it is associated with high mortality. In particular, cardiopulmonary arrest is significantly more common in patients with coronary artery disease, congestive heart failure, COPD, and pneumonia. Although sleep apnea is a risk for respiratory failure, the frequency of cardiopulmonary arrest did not increase significantly [4]. Because of these reasons, discharge from hospital with ventilation support should be done when patients are stable. Additional oxygen needs of the patients should be determined and mechanical ventilation settings should be made. In cases such as progressive COPD or amyotrophic lateral sclerosis (ALS), it may be necessary to switch to invasive ventilation in patients whose permanent ventilation dependence becomes evident. Treatment limitation or palliative care can be planned in line with the patient's life desire [2]. This should be proven by measuring respiratory functions. Therefore, hospital discharge is associated with long-term rehospitalization and mortality risks, which vary according to the need for ventilator support. On the other hand, HMV success is complex and there are many factors that affect this success. Among the factors, the indication for HMV, current stage of disorder, comorbid conditions, likely progression of the disorder, and the level of dependency on ventilator support can be counted. Anticipating problems in order to reduce problems that may occur at home and identifying procedures that can reduce the negative impact of complex home care are important for the long-term success and safety of HMV [5].

38.2 Discussion and Analysis of Main Topics

38.2.1 NIV-Treated Diseases

38.2.1.1 Restrictive Chest Wall Disorders

Hypoventilation and oxygen desaturation can be observed together at night in restrictive chest wall disorders. In addition, these diseases can impair the patient's quality of life due to shortness of breath at night and chronic hypercapnia during the day. NIV can provide significant improvement in a patient's performance and quality of life. On the other hand, it can completely eliminate the symptoms of respiratory failure. Night polysomnography is recommended within 3 months in patients who have severely restricted ventilation due to a restrictive chest wall disorder, but who do not have significant hypercapnia [2].

38.2.1.2 Neuromuscular Diseases

In the neuromuscular disease group, peripheral muscles are usually affected and the situation is important in differential diagnosis. To determine the condition of the respiratory pump muscles, respiratory muscle strength, lung function, and blood gases should be examined. On the other hand, such measurements should be made at regular intervals. If the forced vital capacity (FVC) value is above 70%, polysomnographies and transcutaneous PCO_2 measurement should be performed. Because at the beginning of the disease, hypoventilation may occur in**:** Rapid eye movement (REM) sleep at night [2]. Sung Min Kim et al. have demonstrated that capnography accurately reflected $PaCO_2$ levels and correlated

well with nocturnal respiratory symptoms in patients with amyotrophic lateral sclerosis using NIV. If NIV is started too early in patients with ALS, a feeling of discomfort may occur and impair compliance. Capnography can be used to determine the NIV need of these patients [6].

38.2.1.3 Obesity-Hypoventilation Syndrome (OHS)

Another clinical condition for which NIV is indicated is OHS. OHS is defined as chronic alveolar hypoventilation and daytime hypercapnia ($PaCO_2 \geq 45$ mmHg during rest). Polysomnographic evaluation is mandatory as it can be confused with obstructive sleep apnea. Mortality increases significantly in untreated patients with typical symptoms. Meanwhile, regular polysomnography and blood gas measurements are required.

Oxyhemoglobin saturation decreases during sleep in various lung diseases, and neuromuscular and skeletal disorders. Desaturation is usually greater in REM sleep. In respiratory failure, hypoventilation most commonly emerges initially under conditions of increased activity and/or during sleep, particularly REM sleep.

Becker et al. measured ventilation during sleep in 26 patients with nocturnal desaturation due to different respiratory diseases who have chronic obstructive pulmonary disease (COPD) ($n = 9$), cystic fibrosis (CF) ($n = 2$), neuromusculoskeletal disease ($n = 4$), and obesity hypoventilation syndrome (OHS) ($n = 11$). Hypoventilation has been most prominently observed during REM sleep regardless of the underlying disease. Average V_T values from wakefulness to REM sleep have decreased by 40.9 ± 12.8% in OHS, 31.8 ± 13.3% in COPD, and 46.0 ± 20.9% in other disorder groups. It shows that hypoventilation may be the main factor leading to hypoxia during sleep and that reversing hypoventilation during sleep should be an important therapeutic strategy for these patients.

38.2.1.4 Chronic Obstructive Pulmonary Disease

Out-of-hospital NIV may improve clinical symptoms of blood gas and affected physical exercise capacity in patients with stable COPD and daytime hypercapnia ($PaCO_2 \geq 50$ mmHg). It should also be kept in mind that the initiation of NIV in advanced COPD and according to the above criteria requires a high degree of motivation and cooperation on the patient side. Therefore, as a prerequisite for long-term treatment adherence in patients with often comorbidity, hospitalization should be continued until a stable therapy setting is achieved [2].

38.2.1.5 Stable COPD

NIV can improve survival and reduce hospitalization in selected patients with COPD (daytime hypercapnia, $PaCO_2 \geq 52$ mmHg). Long-term administration of oxygen can improve survival in patients with severe chronic hypoxemia at rest. In patients with stable COPD and moderate exercise-induced hypoxemia, long-term oxygen prescription does not prolong death or first hospitalization or does not provide permanent benefit in health status, lung function, and 6-min walking distance. In addition, altitude can affect patients' oxygen demand. Hypoxemia may deepen while being transferred by air in a patient with sufficient resting oxygenation at sea level.

Rehospitalizations for acute exacerbations of COPD place a burden on the healthcare system. For patients with an acute exacerbation of COPD who were diagnosed with COPD based on spirometric tests and who showed airflow obstruction (FEV 1 / FVC < 70% and FEV 1 > 80%), the rate of rehospitalization within 1 month has been reported as 22.78% [7]. For acute exacerbations of COPD, NIV can be initiated as an acute measure. In these patients, NIV can generally be maintained as home ventilation therapy, but the importance of such a procedure has not yet been conclusively proven. In these patients, blood gas analysis should be performed two weeks after discharge from the hospital, and if hypercapnia persists during the day ($PaCO_2 \geq 53$ mmHg), the NIV indication should be evaluated [2].

38.2.1.6 End-of-Life Care

The use of acute noninvasive ventilation can serve as a flag for considering referral to palliative care services, as it can be valuable for both

active symptom control and end-of-life care. On the other hand, intubation may not be suitable if the patient is in the final stage. In a study conducted in the United States on ARF patients with DNI orders, about half of the patients treated with NIV have survived and have been discharged from the hospital. Patients with congestive heart failure were much better than those with COPD and pneumonia. In addition, in another study on the use of NIV as a "single" palliative measure, NIV has improved dyspnea and has reduced the amount of morphine requirement in end-stage cancer patients faster than oxygen alone [8]. Therefore, the underlying reversible reasons for NIV in patients with DNI orders should be reviewed.

38.2.2 Current Practices in Patient Follow-Up

38.2.2.1 Pulse Oximeter

One of the treatment goals in hypercapnic or hypoxemic respiratory failure during the weaning period from the mechanical ventilator of patients with COPD is to keep SPO_2 in the range of 88–92. Complementary oxygen therapy, the ventilator, suppresses the impulse, increases hypercapnia, and can make the pulse oximeter unusable to monitor the decreases in alveolar ventilation and increases in secretions. If the patient needs high oxygen, it should be kept in mind that home ventilators do not provide more than 50% oxygen in inspiration, and if rapid desaturation develops when the patient leaves NIV, IMV should be considered [9].

38.2.2.2 Capnography and Skin Carbon Dioxide (CO_2)

Capnography and skin carbon dioxide (CO_2) monitoring are useful for demonstrating day and night hypercapnia. Daytime hypercapnia (>44 mmHg) may indicate severe sleep hypercapnia and oxyhemoglobin desaturation of less than 95%. It is important to evaluate whether there is alveolar hypoventilation during the monitoring of patients treated with NIV. The gold standard for this is the evaluation of arterial blood gas. However, this is uncomfortable for patients who are followed up at home. And it requires experienced staff. Transcutaneous capnography, which is recommended in patients with COPD due to undesired mask-induced leakages, allows distinguishing hypoxemia due to ventilation-perfusion incompatibility and hypoventilation [10].

38.2.2.3 Lung and Diaphragm Ultrasonography (DU)

The use of lung ultrasonography (LU) as a predictive tool to evaluate NIV effectiveness is being investigated. More evidence is needed to evaluate hypoxemic respiratory failure. Diaphragm ultrasonography allows direct imaging of the diaphragm muscle and evaluation of its activity. The evaluation of diaphragm thickening fraction (DTF) may be useful in evaluating diaphragm function and its contribution to respiratory workload. Diaphragm movement, which measures the distance the diaphragm can move during the respiratory cycle, can help distinguish diaphragm dysfunction. These two parameters can be a guide in optimizing the ventilator settings [11].

38.2.2.4 Mechanical Insufflation-Exsufflation (MIE)

In patients with neuromuscular and chest wall disease, breathing without a ventilator may not always be provided during or after a respiratory infection attack. However, NIV and MIE may need to be used aggressively during intermediate respiratory tract infection episodes in patients requiring NIV and MIE who are followed-up at home. Therefore, to avoid the need for intubation in these patients, patients with ventilator pump failure and low vital capacity (VC) should be

identified in advance. VC measurement should be performed in both sitting and supine positions. MIE should be provided when the patient's maximum assisted cough peak flows are less than 270–300 L/min [12].

38.3 Conclusion Discussion

There is no guideline defining the criteria for patients being discharged from the acute intensive care unit. Clinicians generally discharge patients who are considered to be at low risk for physiological decompensation. Unplanned intubation often occurs in patients at risk of respiratory failure. Therefore, hospital discharge is associated with long-term rehospitalization and mortality risks, which vary according to the need for ventilator support. Among the factors affecting the success of HMV, the indication for HMV, current stage of disorder, comorbid conditions, likely progression of the disorder, and the level of dependence on ventilator support are important. Out-of-hospital discharge with ventilation support should be done when patients are stable.

Key Major Recommendations

- Supplemental oxygen needs of patients should be determined.
- Capnography can be used to determine the need for NIV in patients with ALS.
- MIE should be provided when the patient's maximum assisted cough peak flows are not sufficient.
- Out-of-hospital discharge with ventilation support should be done when patients are stable.

References

1. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005;25:1025–31.
2. Schäfer H. Außerklinische Beatmung: Lungenerkrankungen. MMW Fortschr Med. 2020;162(7):41–50.
3. Chu CM, Chan VL, Lin AWN, et al. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. Thorax. 2004;59:1020–5.
4. Bedoya AD, Bhavsar NA, Adagarla B, et al. Unanticipated respiratory compromise and unplanned intubations on general medical and surgical floors. Respir Care. 2020;65(9):1233–40.
5. Piper A. Discharge planning and management for patients with chronic respiratory failure using home mechanical ventilation. Breathe. 2010;6:322–33.
6. Kim SM, Park KS, Nam H, et al. Capnography for assessing nocturnal hypoventilation and predicting compliance with subsequent noninvasive ventilation in patients with ALS. PLoS One. 2011;6:e17893.
7. Becker HF, Piper AJ, Flynn WE, et al. Breathing during sleep in patients with nocturnal desaturation. Am J Respir Crit Care Med. 1999;1999(159):112–8.
8. Jennings JH, Thavarajah K, Mendez MP, et al. Predischarge bundle for patients with acute exacerbations of COPD to reduce readmissions and ED visits: a randomized controlled trial. Chest. 2015;147:1227–34.
9. https://www.brit-thoracic.org.uk/quality-improvement/clinical-resources/non-invasiveventilation.
10. Nassar BS, Schmidt GA. Capnography during critical illness. Chest. 2016;149:576–85.
11. Vivier E, Dessap AM, Dimassi S, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med. 2016;38:796–803.
12. https://www.uptodate.com/contents/continuous-noninvasive-ventilatory-support-for-patients-with-respiratory-muscle-dysfunction.

Home Care Ventilator-Dependent Patients

39

Bruno Cabrita, Gil Gonçalves, André Cabrita, and Antonio M. Esquinas

Abstract

Home mechanical ventilation is an increasing treatment choice for patients with chronic respiratory failure, such as chronic obstructive pulmonary disease, sleep disorders, and neuromuscular diseases. It has proven benefits in the reduction of symptoms and hospital admissions, and improved survival and health-related quality of life. Although the benefits are significant for the patient, family, and/or caregivers, there is still uncertainty about the best treatment strategy. More studies are required in this field.

Keywords

Home care · Ventilation · Hypoventilation · Respiratory failure

B. Cabrita (✉)
Pulmonology Department at Hospital Pedro Hispano, Matosinhos, Portugal

G. Gonçalves
Pulmonology Department at Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

A. Cabrita
Cardiology Department at Centro Hospitalar Universitário São João, Porto, Portugal

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

Abbreviations

ALS	Amyotrophic lateral sclerosis
APAP	Automatic positive airway pressure
ASV	Adaptive servo ventilation
AVAPS	Average volume-assured pressure support ventilation
BiPAP	Bi-level positive airway pressure
BMI	Body mass index
CO_2	Carbon dioxide
CompSA	Complex sleep apnea
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
DMD	Duchenne muscular dystrophy
EPAP	Expiratory positive airway pressure
FEV1	Forced expiratory volume in 1 second
FiO_2	Inspiratory oxygen fraction
HF	Heart failure
HMV	Home mechanical ventilation
IPAP	Inspiratory positive airway pressure
IV	Invasive ventilation
iVAPS	Intelligent volume-assured pressure support
LTOT	Long-term oxygen therapy
MIP	Maximal inspiratory pressure
NIV	Noninvasive ventilation
NMD	Neuromuscular disease
O_2	Oxygen
OHS	Obesity-hypoventilation syndrome
OSA	Obstructive sleep apnea

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_39

$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
Pro-BNP	Pro-brain natriuretic peptide
PS	Pressure support
REM	Rapid eye movement
RF	Respiratory failure
ST	Spontaneous timed
USA	United States of America
VC	Vital capacity
Vt	Tidal volume

39.1 Introduction

Home mechanical ventilation (HMV) has a highly variable prevalence, but the number of patients has been progressively increasing. Data from European countries refer to 0.1/100000 patients in Poland, but 10/100000 in Sweden, and an estimated 13% users of invasive ventilation (IV) via tracheostomy. In Canada, the prevalence is 12.9/100000 patients, where 72% receive noninvasive ventilation (NIV) and 18% are ventilated via tracheostomy. In Australia, the prevalence is 9.9/100000 patients, with only 3.1% of patients receiving IV. In the United States of America (USA) there are 11000 patients receiving HMV [1].

In the last few years these numbers have been increasing, along with the increasing evidence and indication to treat patients with HMV. Initially, the main indication was neuromuscular diseases (NMD), but recently there have been an increasing number of patients treated with NIV due to obesity-hypoventilation syndrome (OHS) and chronic obstructive pulmonary disease (COPD). In Australia and New Zealand, 31% of HMV patients are being treated due to OHS, the most common cause, followed by NMD with 30% of cases [1].

In the USA, the prevalence of children under HMV treatment is 4.7–6.4/100000. In this age, there have been increasing cases with indication to HMV and a growing tendency to transition to adulthood with this treatment [1].

39.2 Discussion and Analysis of Main Topics

39.2.1 Indications for Home Mechanical Ventilation

Guidelines recommend the use of HMV for the treatment of chronic respiratory failure (RF). This strategy has proven benefits in the reduction of symptoms related with RF (dyspnea, day-time sleepiness, fatigue), hospital admissions, improved survival, and health-related quality of life. Although the benefits of this treatment are significant for the patient, family, and/or caregivers, there is still uncertainty about the best ventilation strategy [2].

The main indications for HMV are described in Table 39.1 and include COPD, OHS, obstructive sleep apnea (OSA), central sleep apnea (CSA) with Cheyne-Stokes breathing, and NMD [1, 3].

Table 39.1 Indications for home mechanical ventilation [7]

Indications for home mechanical ventilation
Lung diseases
COPD
Bronchiectasis
Cystic fibrosis
Ventilatory disorders
Ondine's curse
Cheyne-Stokes breathing
Obesity-hypoventilation syndrome
Complex sleep apnea
Upper airway abnormalities
Obstructive sleep apnea
Pierre Robin syndrome
Chest wall abnormalities
Kyphoscoliosis
Sequelae of tuberculosis
Neuromuscular diseases:
Amyotrophic lateral sclerosis
Duchenne dystrophy
Myotonic myopathy
Spinal muscle atrophy
Acid maltase deficiency

COPD chronic obstructive pulmonary disease

39.2.1.1 Chronic Obstructive Pulmonary Disease

There are established benefits in the treatment of acute COPD exacerbations with hypercapnia using NIV [4]. On the other hand, the role of HMV in COPD remains controversial, although benefits have been described [2].

Studies regarding the role of NIV combined with long-term oxygen therapy (LTOT) for patients with severe COPD lack in the literature. Previous studies failed to demonstrate benefits probably due to the use of low levels of pressure support, not targeted to improve day-time hypercapnia, and due to its use in patients with borderline chronic RF. Recent investigations were developed with the use of high-intensity NIV (high inspiratory positive airway pressure [IPAP] and high respiratory back-up rate) with the objective of reducing arterial partial carbon dioxide pressure ($PaCO_2$). Studies that used mean IPAP of 28 cmH_2O showed improvements in forced expiratory volume in 1 s (FEV1) with 2 months of treatment. Others showed better adherence with no influence in sleep quality. The concern about high pressures in patients with heart failure (HF) are explained by the increased intra-thoracic pressure applied by the ventilator, with the risk of compromising venous blood return, reduced cardiac output, and increased pulmonary vascular resistance. However, median-term cardiovascular safety has been proved [4]. Current data recommend high-intensity NIV use in patients with stable COPD and hypercapnia [1].

The benefits of HMV in post-exacerbation COPD patients remain controversial and unclear since many patients improve without this treatment [1]. COPD patients who have persistent hypercapnia after exacerbation and require NIV have a worse clinical outcome than others who return to a state of eucapnia, in terms of hospital readmission (40% 90-day readmission rate) and mortality (50% 1-year mortality). This group of patients might benefit from HMV with supplemental oxygen therapy [4].

Some patients with COPD are obese and may develop OSA, defined as COPD-OSA overlap. There are many factors in COPD that contribute to obesity and OSA development, including low levels of physical activity and corticosteroid therapy. The prevalence of obesity varies from 15% in Europe and 54% in North America, and, paradoxically, there seems to be a protective effect in lung function and survival. COPD patients with chronic bronchitis and cor pulmonale are more likely to develop OSA, since they tend to have higher body mass index (BMI) and a shift of fluid in supine position, in contrast with emphysematous phenotype. Patients with untreated COPD-OSA overlap have worse prognosis than COPD alone, with 9-year mortality of 42% and 24%, respectively. The first-line treatment for these patients is continuous positive airway pressure (CPAP). NIV should be reserved for COPD patients that have more significant hypercapnia, a suboptimal response to CPAP or after an exacerbation with decompensated RF. Predictors of CPAP failure include daytime hypercapnia and nocturnal hypoxemia (oxygen saturation < 90%). In patients treated with NIV, the levels of expiratory positive airway pressure (EPAP) are superior to COPD patients alone. The optimal strategy of ventilation in patients with COPD-OSA overlap is currently unknown and guidelines recommend polysomnography study to guide treatment [4].

Other phenotype of COPD patients may exhibit episodic rapid eye movement (REM) nocturnal hypoventilation without severe daytime hypercapnia ($PaCO_2 < 55$ mmHg). These patients have higher risk for developing pulmonary hypertension and COPD exacerbations. Studies with 1-year treatment using NIV in these patients showed reduction in exacerbation rate, but more evidence is required [4].

In patients with severe COPD, palliative care is a crucial part of the best treatment, and it may include HMV combined with supplemental oxygen therapy in selected patients [4].

39.2.1.2 Obesity-Hypoventilation Syndrome

OHS was first described in 1956. Despite these years, there is still uncertainty about the pathogenesis of this disorder. OHS is defined as the combination of obesity (BMI $\geq$30 kg/m^2), daytime hypercapnia and respiratory changes during sleep, in the absence of other causes of hypoven-

tilation. It is multifactorial and characterized by impaired lung mechanics and respiratory muscle dysfunction. The prevalence of OHS in obese patients is currently unknown, but in obese patients with OSA varies between 10% and 20%. Obese patients with OHS have increased mortality [5].

The treatment of OHS requires CPAP, or NIV in cases of suboptimal response. NIV treatment in these patients has shown improvements in blood gases, polyglobulia, respiratory function, reduction of hospital admissions, and improved quality of life and survival [5]. Despite these benefits of HMV, the best treatment must also include rehabilitation, weight-loss support, and consider the referral for bariatric surgery [1].

39.2.1.3 Chronic Heart Failure

HF is a life-threatening condition with high socioeconomical burden; therefore, it should be considered a global health priority. It affects 1–2% of developed countries' population. It reduces functional capacity, quality of life, and has poor prognosis [6].

The main symptoms of HF include exertional dyspnea and fatigue, with limitation in daily life activities, and progression to dyspnea at rest in severe cases. Chronic HF shares common risk factors with chronic lung diseases, particularly smoking. Therefore, many patients with chronic obstructive lung diseases also have chronic HF [6].

The best ventilatory strategies to treat patients that have RF and chronic HF include CPAP and bi-level positive airway pressure (BiPAP) therapy. In these patients, CPAP improves cardiorespiratory performance by increasing functional residual capacity, recruiting collapsed alveoli, decreasing right-to-left intrapulmonary shunt, improving oxygenation, and lung compliance. Also, CPAP has shown improved survival, and decreased health care readmissions, length of stay, and costs. The ideal CPAP pressure is still unknown. Some authors use 6 cmH_2O to improve patients' tolerance and cardiac output; others use 10 cmH_2O for better alveolar recruitment and effective blood gases exchange; still others use less than 6 cmH_2O with benefits in exercise tolerance and improved adherence [6]. The use of BiPAP in these patients has the advantage of improving exercise tolerance, relieving cardiac stress, and improving cardiac function. Pressure support (PS), the difference between IPAP and EPAP, unloads respiratory muscles and improves exercise endurance. A PS of 5 cmH_2O reduces transmural pressure gradient and increases cardiac output, therefore, improving exercise capacity and enhancing the cleaning of carbon dioxide (CO_2) and waste metabolites [6].

CPAP improves outcomes in patients with OSA and HF. In the treatment of CSA with HF, the best treatment remains controversial [1]. Currently, routine use of adaptive servo ventilation (ASV) to treat sleep disturbances is contraindicated if the patient has symptomatic HF (NYHA >II) with left ventricular ejection fraction <45% [1, 6].

COPD patients typically have cardiovascular comorbidities. NIV treatment of patients with chronic RF has shown positive effects, reducing systemic inflammation and pro-brain natriuretic peptide (pro-BNP). The use of high positive pressures may raise the concern of decreasing cardiac output in patients with HF; however, studies with 3-months therapy in COPD patients showed it is a safe approach. Treatment with high-intensity NIV (respiratory rate 20–22 breaths/minute) and low-intensity NIV (respiratory rate < 12 breaths/minute) in stable COPD patients have both shown improvements in exertional dyspnea, lung function, and health-related quality of life. However, high-intensity NIV tends to have better outcomes in gas exchange. If the patient has chronic HF, the adoption of a low-intensity NIV might be less harmful. Despite the preferred strategy, NIV must be used with caution in patients with COPD and HF, and cardiac function should be checked regularly [6].

39.2.1.4 Sleep Disorders

Patients with chronic RF commonly have sleep disturbances and nocturnal hypoventilation. Sleep disturbances are frequent in modern society. Studies report a pathological apnea-hypopnea index (≥5/h) incidence of 9% in healthy women and 24% in healthy men [3].

During the REM phase of sleep, changes in $PaCO_2$ and arterial partial pressure of oxygen (PaO_2) occur. Vt decreases and consequently also does minute ventilation. Therefore, patients with chronic RF frequently have deoxygenation and hypercapnia during REM sleep, where airway resistance also increases. Sleep tends to be more fragmented, with more arousals, and patients describe daytime fatigue and impaired concentration. Hence, adequate treatment with HMV is crucial to improve sleep quality, gas exchange, daytime symptoms, and quality of life [3].

Sleep disorders with indication for HMV include OSA, complex sleep apnea, disorders associated with cardiac dysfunction, and OHS [7].

OSA is characterized by recurrent episodes of upper airway obstruction during sleep, partial (hypopnea) or complete (apnea), causing arousals and desaturation, and its incidence is 4% in men and 2% in women. Symptoms include daytime sleepiness, fatigue, difficulty in concentration, memory-loss, and loss of sleep quality due to frequent arousals, choking, and awakenings. Its complete pathophysiology remains unknown, but it is acknowledged that obesity plays an important role in the obstruction of the upper airways due to infarction of the tongue and/or dilation of the muscles of the pharynx. Sleep time promotes these episodes due to the supine position, since the tongue tends to occlude the rear wall of the oropharynx and increase the risk of airway occlusion. Long-term outcomes of untreated disease include the development of hypertension, coronary artery disease, stroke, and sudden death. The risk of traffic accidents due to sleepiness is also highly increased. Treatment of this disorder includes CPAP therapy, shown to improve sleep quality, resolution of the airway obstructions, improved cognitive function, cardiovascular morbidity, and mortality [7].

In patients under treatment for OSA a particular complication might occur, designated by complex sleep apnea (CompSA). CompSA defines the development of central apneas in a patient with OSA under treatment with CPAP. The obstructive events are resolved (<5 events/h) but central events are >5/h. The first approach should be to evaluate if CPAP pressures are too high and causing pressure toxicity. If so, it is advised to decrease the pressure, if possible, assuming a permissive flow-limitation that allows a mild degree of airway obstruction without increasing the risk of central apneas development. The addition of supplemental oxygen therapy may help control hypoxic ventilatory response. Other strategy is the implementation of BiPAP therapy in spontaneous-timed (ST) mode [7].

CSA is a sleep disturbance often associated with a periodic breathing pattern, Cheyne-Stokes breathing, in patients with chronic HF. CSA is characterized by a cessation of respiratory drive during sleep, without respiratory movements (in contrast to OSA), causing RF and worsening of patients' prognosis, if untreated. The main risk factors for CSA are male gender, hypocapnia, atrial fibrillation, and older age. Treatment with CPAP and BiPAP is often suboptimal and ASV might be required [7].

Studies regarding IV in home-care setting and its influence in sleep quality still lack in the literature [3].

39.2.1.5 Neuromuscular Diseases

Many NMD have indication for treatment with HMV, and NIV is considered standard practice in these patients. They include amyotrophic lateral sclerosis (ALS), muscular dystrophy, and others. Treatment benefits include prolonged survival, symptom relief, and reduced hospital admissions [1, 2, 8]. The combination of NIV and cough-assist is crucial to prevent the expected outcomes of the disease that include recurrent respiratory infections and the need for tracheostomy ventilation [1].

The study of patients with NMD should always include respiratory functional parameters that help physicians decide the best timing to start treatment. They consist of the following:

Pulmonary function tests: Vital capacity (VC) is valuable to decide the beginning of NIV in NMD patients. When VC <50% of the predicted value, there is indication to start the therapy. In patients with diaphragm weakness, supine VC is a more useful indicator compared with standard erect VC [8].

Maximal inspiratory pressure (MIP) is also indicative of the necessity of NIV, when its value is less than 60cmH_2O. Another measure for inspiratory pressure capacity is the sniff test, which measures the generated nasal pressure in one nostril during a sniff manouvre [8].

Nocturnal oximetry: The evaluation of nocturnal desaturation with oximetry may help diagnose nocturnal hypoventilation [8].

Polysomnography: Sleep study with polysomnography is useful in NMD to help identify the need for NIV and ideal ventilatory parameters [8].

There is recommendation for the beginning of NIV in the treatment of NMD patients when they have symptoms (fatigue, dyspnea, morning headaches) and $PaCO_2 \geq 45$ mmHg, or nocturnal desaturation of ≤88% during five consecutive minutes, or VC <50% predicted, or MIP <60 cmH_2O. Other indications include support during gastrostomy tube placement, IV extubating, and in patients submitted to tracheostomy who were successfully decannulated [8].

39.2.1.6 Other Indications

HMV may have a role in facilitating discharge for hospitalized patients, preserving the best treatment and improving their independence in daily-life activities in an outpatient setting [2].

Another interesting field for the use of NIV is to improve exercise tolerance during a pulmonary rehabilitation program [9].

39.2.2 Home-Mechanical Ventilation Equipment

HMV can be offered to patients through different forms and settings, including tracheostomy tube (IV) or NIV with a mask. A wide range of ventilators are available and the basic knowledge of their functioning and indications is essential to allow physicians provide the best treatment for their patients [10].

A ventilator transforms energy input into a mechanical output that includes a desirable pressure, flow, or volume. It can apply positive pressure in the airways to assure its patency or generate negative pressure to apply externally on the chest and assist the coughing process (cough-assist) [10].

Ventilators are constituted by a respiratory circuit, a pneumatic system, inspiratory and expiratory valves, controlled variables (trigger, limits, cycling), different modes of mechanical ventilation, interface, alarm system, monitoring system, and some accessories. User interfaces are highly variable and include facial masks, nasal masks, mouthpieces or tracheostomy tube. The type of circuit also may differ and include single-limb (single tube for inspiration and expiration that requires a non-rebreathing expiratory valve or a vented system to prevent CO_2 rebreathing) or double-limb (different inspiratory and expiratory tubes) devices [10].

Many home-care ventilators have a low-pressure oxygen (O_2) inlet, although this oxygen delivery system is not constant and the inspiratory oxygen fraction (FiO_2) cannot reach 100%, if desired [10].

All home-care ventilators are equipped with long-lasting internal batteries, usually with short charging time. These batteries' autonomy may last 3–9 h of utilization, depending on the defined parameter settings [10].

Ventilator accessories include heated humidifiers, carriers, and filters [10].

39.2.3 Home-Mechanical Ventilation Modes

Home ventilators have multiple forms of ventilatory assistance, and recent devices for life-support are prepared to work in volume and/or pressure-controlled modes [10].

Some modalities of ventilatory support include:

CPAP: Currently it is the preferred mode of ventilation for the treatment of OSA and acute hypoxemic RF in patients with chronic HF. CPAP consists in the application of constant positive pressure in spontaneous breathing patients [7].

Automatic Positive Airway Pressure (APAP): APAP delivers a self-titrating positive airway pressure, using algorithms that detect variations

in the degree of airway obstruction, thus, self-adjusting the required pressure to assure patency. It may be used during a polysomnography to titrate the ideal CPAP pressure to treat OSA. Currently, APAP treatment is only advised in patients with OSA or respiratory events related with position. It is not recommended in patients with other comorbidities, such as chronic HF, COPD, CSA, or hypoventilation [7].

BiPAP: BiPAP is a ventilation mode that includes IPAP and EPAP. The main indications for its use are disorders that result in hypoventilation (OHS, NMD) and sleep disturbances (OSA, CSA). Patients with OSA who do not tolerate high CPAP pressures may be candidates for treatment with BiPAP. The IPAP assists inspiration and reduces work of breathing and fatigue. The EPAP assists expiration, maintaining airway patency and improving functional residual capacity. The PS (difference between IPAP and EPAP) is important to maintain alveolar ventilation and to reduce $PaCO_2$ [7].

Auto-BiPAP: This is a recent device with automatic adjustment of IPAP and EPAP, providing greater treatment flexibility in pressures changes [7].

ASV: ASV is used in the treatment of CSA with Cheyne-Stokes breathing pattern. It is a complex mode of ventilation that delivers EPAP to treat obstructive apneas and automatically adjusted IPAP to maintain a target ventilation, aiming to stabilize breathing patterns and reduce respiratory alkalosis that triggers central apneas [7].

Average Volume-Assured Pressure Support Ventilation (AVAPS): AVAPS delivers self-adjusted pressure to the airways, aiming to maintain a target Vt. It is used in patients with chronic hypoventilation, including OHS, NMD, and COPD. The main advantage of this ventilation mode is that it guarantees the desirable Vt and automatically adjusts pressures as the disease progresses, making it useful in NMD like ALS [7].

Pressure ventilatory support allows better non-intentional leaks compensation, compared with volume support. However, tidal volume (Vt) may not be guaranteed with pressure support, but only with volume support. AVAPS is a hybrid mode of ventilation that works with both pressure and volume control. The compensation of non-intentional leaks depends on the "vented" or "not-vented" circuit [10].

Intelligent Volume-Assured Pressure Support (iVAPS): Recently, other modes of ventilation support, known as iVAPS, are able to assure a target alveolar ventilation [10].

Sighs: This mode of support has increasing interest. It allows the definition of volume or pressure sighs, their frequency, and amplitude. Although studies are lacking, recent clinical trials demonstrated improved oxygenation with this recruitment maneuver in patients with acute RF [10].

Mouthpiece Ventilation: This is a useful interface in patients with NMD that require NIV 24 h/day, such as end-stage Duchenne muscular dystrophy (DMD) [10].

39.2.4 Monitoring of Home-Mechanical Ventilation

Home-care ventilators are equipped with monitoring display, allowing users the direct visualization of ventilatory parameters, including non-intentional leaks and pressure/volume waveforms which inform about patient-ventilator interaction [10].

HMV monitoring strategies may vary. There are three main systems of telemonitoring:

First-generation system: Data from ventilators are transferred via a telephone system to the clinical team database [1].

Second-generation system: Data transfer from ventilators is synchronous with an automated algorithm but has the risk of compromising immediate decisions by the clinical team, if monitoring only occurs at certain times [1].

Third-generation system: This has constant decision-making support with monitoring centers constituted by physicians and specialist nurses with full authority to effect therapy changes, 24 h/day, every day [1].

Telemonitoring is fundamental to assist patients and provide the best possible care.

Studies demonstrate that telemonitoring is associated with higher treatment compliance, less hospital admissions, improved quality of life, and reduced healthcare costs [1].

The ventilation interface should always be optimized in order to reduce non-intentional leaks since it is associated with worse sleep quality. Polysomnography should be performed to assess suboptimal treatment results and improve ventilator settings [3].

Patients' opinion about their home ventilators must be taken into account in the monitoring process. Although there are studies lacking regarding this subject, it seems reasonable to assume that a patient who is comfortable with his ventilator has higher adherence and, therefore, improved outcomes and prognosis [10].

Further investigation on HMV is still required in order to define clear recommendations and guidelines on telemonitoring-assisted HMV [1].

39.3 Conclusion

HMV has significant benefits in the treatment of ventilation-dependent patients, improves quality of life, and reduces healthcare costs and hospital admissions. The main indication is the treatment of chronic RF and includes different etiologies, such as NMD, COPD, and sleep disorders. Patients' opinion about their home ventilators should always be taken into account in the monitoring process to improve treatment adherence and outcomes.

Areas of future research include improvements in tele-medicine in order to define the best treatment, monitoring, and follow-up strategies for these patients.

Key Major Recommendations

- HMV has significant benefits in the treatment of chronic RF.
- The main indications for HMV include NMD, COPD, and sleep disorders.
- Patients' opinion about their home ventilators should always be taken into account.
- More investigation into tele-medicine and tele-monitoring is required.

References

1. Simmonds A. Home mechanical ventilation: an overview. Ann Am Thorac Soc. 2016;13(11):2035–44.
2. Povitz M, Rose L, Shariff S, et al. Home mechanical ventilation: a 12-year population-based retrospective cohort study. Respir Care. 2018;63(4):380–7.
3. Schwarz S, Magnet F, Windisch W. Impact of home mechanical ventilation on sleep quality. Curr Opin Pulm Med. 2017;23:500–5.
4. Suh E, Murphy P, Hart N. Home mechanical ventilation for chronic obstructive pulmonary disease: What next after the HOT-HMV trial? Respirology. 2019;24:732–9.
5. Castillejo E, Ramos P, Martin S, et al. Noninvasive mechanical ventilation in patients with obesity hypoventilation syndrome. Long-term outcome and prognostic factors. Arch Bronconeumol. 2015;51(2):61–8.
6. Ciobanu L. Non-invasive ventilation in chronic heart failure, an important comorbidity of COPD. Pulmonol Respir Med. 2018;7(6):416–23.
7. Nicolini A, Banfi P, Grecchi B, et al. Non-invasive ventilation in the treatment of sleep-related breathing disorders: a review and update. Rev Port Pneumol. 2014;20(6):324–35.
8. Hess D. Noninvasive ventilation for neuromuscular disease. Clin Chest Med. 2018;39:437–47.
9. Simonds A. Home ventilation. Eur Respir J. 2003;22(47):38s–46s.
10. Gregoretti C, Navalesi P, Ghannadian S, et al. Choosing a ventilator for home mechanical ventilation. Breathe. 2013;9(5):394–408.

40 Home Noninvasive Ventilation: Lung Function Tests and Telemedicine

Ana Luísa Fernandes, Márcia Araújo, Sara Dias, and Bruno Cabrita

Abstract

Patients under home mechanical ventilation (HMV) are increasing across the world and are associated with elevated costs and difficulty in discharge. Therefore, it is crucial to provide a regular follow-up programme. Lung function tests have an important role for diagnosis and follow-up of respiratory and neuromuscular disorders. Recently, home programmes and telemonitoring have emerged as possible useful options to combine with the "standard care" to provide better supervision in HMV.

Keywords

Home mechanical ventilation · Noninvasive ventilation · Telemedicine · Lung function tests · Home care

Abbreviations

ABG	Arterial blood gas
ALS	Amyotrophic lateral sclerosis
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRF	Chronic respiratory failure
ELBG	Ear lobe blood gas
ER	Emergency department
$etCO_2$	End-tidal carbon dioxide
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HMV	Home mechanical ventilation
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
MEP	Maximum expiratory pressure
MIP	Maximal inspiratory pressure
NIV	Noninvasive ventilation
$PaCO_2$	Arterial carbon dioxide tension
PaO_2	Arterial oxygen tension
PCF	Peak cough flow
RMS	Respiratory muscle strength
SNIP	Sniff nasal inspiratory pressure
T_cCO_2	Transcutaneous carbon dioxide

40.1 Introduction

The overall prevalence of home mechanical ventilation (HMV) in Europe is around 6.6/100,000 and it is rising; however, this varies greatly between countries [1]. The increasing prevalence of severe chronic obstructive pulmonary disease (COPD) and severe obesity, the better identification of adult neuromuscular diseases and the growing lifespan of the general population point to a major increase in the disease burden associ-

A. L. Fernandes (✉) · M. Araújo · S. Dias · B. Cabrita
Pulmonology Department, Hospital Pedro Hispano, Matosinhos, Portugal

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_40

ated with chronic respiratory failure (CRF) in the following years.

HMV is a well-established treatment in some diseases that cause CRF, such as amyotrophic lateral sclerosis (ALS), as it increases survival and prevents hospital admission. However, the use of chronic long-term noninvasive ventilation (NIV) in COPD is still discussed, as it seems that the addition of NIV improves survival when it is aimed to reduce significantly arterial carbon dioxide tension ($PaCO_2$) [2].

Nevertheless, there is no universal consensus regarding what type of follow-up programme would be most effective in chronic patients and the organization of HMV differs widely among countries. Some countries refer these patients to a limited number of respiratory care units for initiation and follow-up, but in other countries there is a larger number of outpatient departments and they report to a national organization. In addition, some countries may offer visits by a healthcare team; however, this is not a universal reality. Moreover, there are other challenges when providing HMV, including the need of a multidisciplinary team, setting to initiate NIV (hospital or home), type of patient-professional contact, patient mobility, reimbursement policy, type and variables to be measure during follow-up as well as patients and caregiver training and cooperation [3].

Recently, another question that accompanies HMV is the development and utility of telemonitoring technology. With the increasing number of HMV patients and difficulties associated with hospital discharge, telemonitoring seems to be an opportunity that offers early remote detection of signs and symptoms of clinical decompensation, remote monitoring of ventilator settings and education reinforcement for the patient and caregiver [4].

Therefore, in the next this chapter, we will review the evidence for evaluation of lung function, home care and usage of telemedicine in patients under HMV.

40.2 Discussion and Analysis of Main Topics

40.2.1 Pulmonary Function Test in HMV

Some healthcare professionals may believe that the evaluation of patients with CRF necessitating HMV requires no more than measurement of arterial blood gas (ABG) to obtain oxygen (PaO_2) and carbon dioxide (CO_2) values. However, a detailed physiological assessment of the key areas of the respiratory system is often appropriate. In one hand, it helps confirm that the correct diagnosis for the cause of CRF is made, as the initial management of a neuromuscular patient may be different from a COPD patient. On the other hand, lung function may be crucial for patient follow-up because it influences treatment decisions and is a prognostic marker in some diseases.

40.2.1.1 Gas Exchange

ABG analysis is an important tool to evaluate gas exchange in the assessment of patients receiving HMV. The results are rapidly available allowing prompt clinical decisions mainly related to ventilation parameters. It is also possible in some centres to use arterialized ear lobe blood gas (ELBG) as an alternative to ABGs as it appears to reflect $PaCO_2$ accurately and can be less painful. Nonetheless, ELBGs can be a less faithful reflection of PaO_2 [4, 5].

Medical devices are evolving to become less invasive and more comfortable for the patient. There are two different techniques for noninvasive $PaCO_2$ monitoring currently being used in clinical practice: the end-tidal carbon dioxide ($etCO_2$) and the transcutaneous PCO_2 (T_cCO_2) measurements. However, end-tidal carbon dioxide measurements seem to correlate poorly with $PaCO_2$ levels, particularly in patients with airways disease. Several studies have demonstrated that transcutaneous measures of CO_2 are

reliable and offer a pain-free method [4, 6]. But, there are two drawbacks: the measurement performed by electrochemical sensors requiring a temperature increase may cause burns in long-term monitoring and there is a 2-min lag time for $PaCO_2$ changes to be reflected in T_cCO_2. The appearance of optical sensors in the market has resolved the burn problem by the electrochemical sensor [6]. Moreover, some systems can also be portable, which makes possible a $TcCO_2$ evaluation during a home visit by the healthcare professionals.

Portable oximetry is also a valuable tool for patients under HMV. In case of clinical deterioration, it may allow trained caregivers and patients to quickly evaluate oxygen status and the need to search for medical aid. Additionally, it may also be useful when neuromuscular patients are being initiated in mouthpiece ventilation to use it when there is a desaturation until they feel accustomed to this ventilatory mode. Some devices can be connected to the ventilator-monitoring system to provide oxygen data during the night or greater periods in patients more dependent of ventilation [4]. Finger pulse oximeters may be uncomfortable to wear during large intervals, such as 24 h oximetry, but the same measurement may be performed in a different body part such as the wrist or earlobe [4, 6].

A new trend in the market is a non-contact measurement using a camera or a mobile phone [4, 6]. This technology is based on photoplethysmography imaging and requires that a small area of skin is placed in front of the camera for a few seconds. It obtains peripheral oxygen saturation, heart rate and respiratory rate. The interest in this technology is increasing as it seems particularly suited for home application.

40.2.1.2 Pulmonary Mechanics

Basic spirometry, used to measure forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), is the most commonly encountered measure of pulmonary mechanics and is useful to support the cause of CRF and to monitor progression of a range of diseases including COPD. It has also been demonstrated to be predictive of survival in some disorders, including ALS [4].

As patients become progressively more dependent, home visits and telemonitoring of lung function may be a valuable option. There are portable spirometers or tele-spirometers in the market that allow measurements of FVC and FEV_1 during home visits or by distance with devices connected to a smartphone. Some authors have also used consecutive peak expiratory flow values for follow-up of patients under HMV accompanied by questionnaires during home visits or at distance [4]. However, these options require patient cooperation, specific manoeuvres (not spontaneous breathing) and still are not available worldwide.

A detailed review of lung volumes may be useful for initial diagnosis confirmation and prognostic evaluation in some diseases. Nevertheless, specific devices, which are not easily transportable, are needed for evaluation. Therefore, it is a less convenient option for follow-up of patients under HMV who are progressively becoming more dependent.

Regarding more dependent and severe patients, another important aspect to take into consideration is the progressive difficulty in performing the necessary manoeuvres for lung function evaluation. The forced oscillation technique is a noninvasive method that employs small-amplitude pressure oscillations superimposed on the normal breathing, and it does not require the performance of respiratory manoeuvres. As it does not need patients' cooperation, it is an attractive test to use in home settings [6, 7].

The exhaustive measurement of pulmonary mechanics demands the use of invasive equipment, and it is not available in all lung function laboratories. The pressure transducers needed require invasive catheters that must be inserted in the oesophagi as a surrogate to pleural pressure. After this, several mechanical variables may be obtained, as, for example, compliance, positive end-expiratory pressure and work of breathing. The detailed definition of these pulmonary variables has been previously addressed in this book.

40.2.1.3 Respiratory Muscle Function

The change in vital capacity from sitting to supine is a simple test of respiratory muscle strength (RMS). However, as previously stated in

this book, more specific tests, including sniff nasal inspiratory pressure (SNIP) and maximal inspiratory pressure (MIP), are available. Both these pressure measurements can be performed using handheld devices with a nasal bung or mouthpiece, respectively.

Additionally, expiratory muscle function may be assessed noninvasively using maximum expiratory pressure (MEP) with a pressure measured at the mouth during a forced expiration. MIPs and MEPs have a wide range of normal values and are dependent on the patient's ability to perform the manoeuvre correctly. Therefore, low readings should be interpreted with caution and sometimes multiple tests may be required to assess RMS adequately and exclude muscle weakness in symptomatic patients [4].

Peak cough flow (PCF) is another simple test to evaluate the expiratory muscle function and it is usually performed using a standard peak flow meter. This is usually easily performed in a home visit, and it is a crucial evaluation in neuromuscular disorders. Patients with PCF inferior to 180–200 L/min have been shown to be unable to clear secretion in an adequate way [4]. Thus, these patients usually need manual physiotherapy and use insufflation-exsufflation devices to improve the ability to cough.

In an equivocal clinical case, invasive measurement of RMS may be performed. However, this is frequently used previously to help in the diagnosis, and, consequently, it is not usually necessary in patients under HMV. Moreover, these tests require specialized equipment and are not possible to perform at home. For these reasons, it is not an attractive test for the follow-up of any patient.

40.2.1.4 Overnight Monitoring

The use of nocturnal oximetry in the assessment of HMV can provide the clinician with valuable insights into the severity of disease and efficacy of the prescribed ventilator parameters without requiring the patient to be admitted into the hospital for full physiological monitoring studies. $TcCO_2$ can also be performed at home in more dependent patients, and it is an important tool to evaluate the persistence of nocturnal hypoventilation and efficacy of treatment in patients under mechanical ventilation [4, 8].

Cardiorespiratory polygraphy or a full polysomnography with electroencephalogram monitoring is rarely required in HMV management, although it can be useful if it is desired to elucidate the cause of persistent sleepiness or symptoms despite therapy as well as diagnosing synchronization issues between the patient and the ventilator. These studies may be essentially used for the initial titration of HMV, accordingly to the organization of each hospital [4].

40.2.1.5 Systems for Continuous Monitoring of Breathing

Systems for continuous monitoring breathing can be divided in wearable devices or non-wearable devices. The wearable devices derive physiological variables such as tidal volume, heart rate, minute-ventilation or respiratory frequency from analysing body surface motion detection using specific bands, sensors or patches to measure these differences/body movements. The wearable devices may be respiratory inductance plethysmography, resistance-based sensors, capacitance-based sensors, inertial measurements units by an accelerometer and fibreoptic sensors [6].

Regarding non-wearable devices, most of the options used have already been described in this chapter, such as pulse oximetry, $TcCO_2$ and polysomnography. Another example is the existence of commercial devices that calculate respiratory rate via the detection of pressures changes in the oxygen line in patients under long-term oxygen therapy [6]. Finally, an additional device that can give information on breathing is the home ventilator, as the majority of models allows to analyse or to download data over the previous weeks or months regarding compliance, leaks, tidal volume, minute-ventilation, respiratory rate, percentage of inspirations triggered by the patient and apnoea-hypopnoea indexes. However, reliability of these measures may be limited. Most noninvasive ventilators tend to underestimate the tidal volume delivered, especially with high inspiratory positive airway pressure (IPAP) levels and significant leaks [8]. Furthermore, the clinical relevance of measuring these parameters has not been thoroughly investigated.

40.2.2 Physical Activity

Sedentarism in patients with respiratory or neurologic disorders is a "vicious cycle" as constitutional and respiratory symptoms related to the disease lead progressively to a decrease in exercise capacity and quality of life. Therefore, stimulation of physical activity is also a crucial part of the treatment of patients under HMV. Objective methods to quantify physical activity are usually based on the measurements of metabolic cost, heart rate, body temperature or biomechanical effects (such as acceleration, velocity and displacement). This technology is usually divided into sensor-based, vision-based and radio-based devices. The most known sensor-based devices are accelerometers (the base of actigraphy) and gyroscopes. The video-based recognition system includes a camera, but it restricts the activity of the patients to the limited range of the camera. The radio-based devices normally use radiofrequencies to detect activity and positions [6].

Nowadays, pedometers or counting step functions on mobile phones are easily available and have been proposed as motivational tools for people wanting to increase their physical activity [6].

Therefore, there are several options to stimulate physical activity in patients under HMV. Some patients under HMV have severe illnesses with significant oxygen desaturation, mobility limitation and decreased exercise capacity. A respiratory rehabilitation programme is a valid option for these patients to improve physical activity and to educate them on how to do it in a safe manner at home.

40.2.3 Home Care and Telemedicine in HMV

40.2.3.1 Initiation of Home NIV

One important question that remains unanswered is if it is safe to initiate NIV at the patients' home. Home initiation of NIV would greatly alleviate the burden on the healthcare system and would prevent demanding hospital visits in a disabled dyspnoeic patient population. Nonetheless, it needs to be proven safe, effective and cost-effective. In patients with neuromuscular disease, obesity-hypoventilation and thoracic wall restrictive disease, it has been demonstrated that initiation of chronic NIV at home, with the use of telemonitoring, is non-inferior to initiation in the hospital [8, 9].

Recently, Duiverman MJ et al. published the first study showing that home initiation of NIV in stable hypercapnic COPD patients using telemedicine is non-inferior to in-hospital initiation [10]. However, these studies have some limitations like the small number of participants, being a single centre experience and the need of technology/professionals that are not available in every hospital. Therefore, more studies are necessary to evaluate the potential clinical and economical benefits of HMV initiation. Improvements in the technical and digital opportunities, during the last couple of years, will facilitate the development of future telemonitoring studies.

40.2.3.2 Follow-up of Patients Under HMV

There is no universal consensus regarding what type of follow-up programme would be most effective in chronic patients under HMV. Is it better a regular visit to the outpatient clinic? Or a follow-up with home visits by a trained team in NIV? Or a combination of both? Probably a one size fits all will not be possible in this area. In one hand, as patients become more ventilator dependent, it is progressively more difficult to dislocate to the hospital. On the other hand, the most cited traditional home care programmes are based on home visits by specialized nurses or respiratory therapists [4]. Though, it presents some limitations such as the number of patients who can be included, costs, distance and time needed to reach the patient's home. Hence, some groups have published their version of home care for mechanical ventilated patients, most including a combination of multiple variables such as self-management, education of patients and caregivers, available telephonic contact with the team, outpatient visits and home visits by dedicated staff and using of telemedicine technology for follow-up.

The clinical surveillance of patients under mechanical ventilation is a complex process as it may involve a large number of healthcare professionals, a substantial number of variables that can be measured and the different settings where it can occur (Fig. 40.1).

The primary goal of the follow-up in HMV, either in-hospital, at the patient's home or by phone, should be to evaluate if the overall effect of HMV is both beneficial and tolerable to the patient. Firstly, a clinical interview should be systematically performed addressing the persistency or resolution of symptoms using standardized questionnaires, exacerbations, need of hospital admissions, adherence and adverse effects of NIV. Secondly, most home ventilators have internal monitoring clocks that measure and record the total 'blower' hours with data cards that can be used for the measurement of adherence. These data should be compared against the patient reported adherence and any discrepancies discussed with the patient and caregivers. Poor adherence should prompt further questioning to identify areas to improve compliance. Furthermore, a key role for the success of HMV is the caregiver and, consequently, it is of utmost importance to question about its well-being and needs. Another important position is the external respiratory company that provides the device and, in some countries, accompanies the patient stimulating adherence and does also the maintenance of the ventilator and masks. After the initial assessment, several exams may be performed to understand the cause of symptoms or problems reported by the patient and/or caregiver.

Another important question is how often patients should be contacted by phone or visited by the home care team or at the hospital and what variables should be measured during these visits. Which patients may benefit more from a tool, such as telemonitoring? Unfortunately, there are countries where home care is not a reality. Moreover, as previously stated, published data offer several different care protocols with different inclusion criteria and disease severity as well as the tools measured during clinical evaluation. Therefore, no standard recommendation may be made on how or when to visit; however, reduction in hospitalisation and use of other acute healthcare services reduction in mortality rate, improvement in the sickness impact profile scores and patient satisfaction have all been

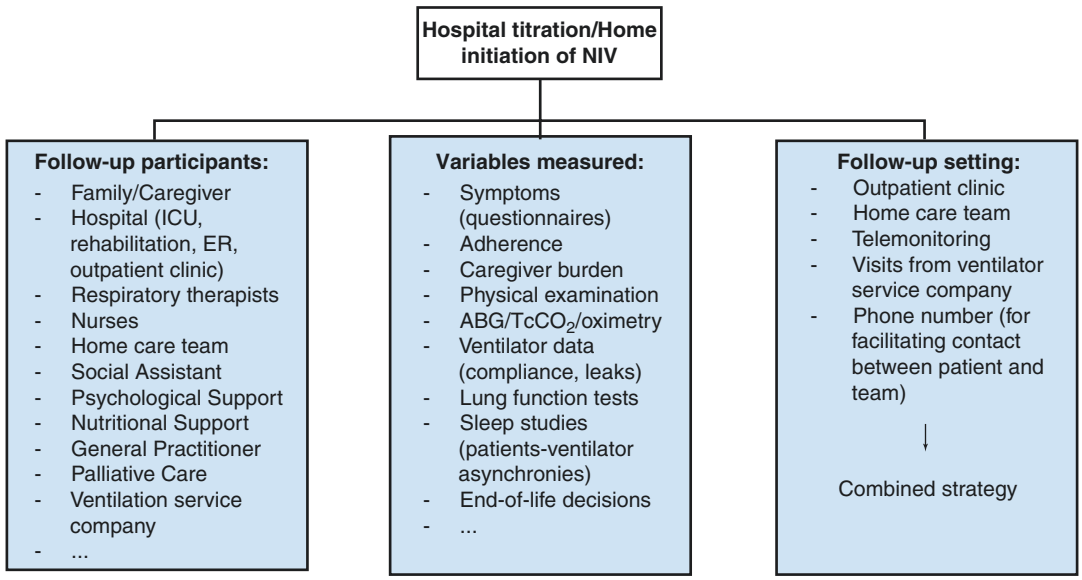

Fig. 40.1 The participants, variables measured, and settings needed for home mechanical ventilated patient's follow-up. (*NIV* noninvasive ventilation, *ICU* intensive care unit, *ER* emergency department, *ABG* arterial blood gas, $TcCO_2$ transcutaneous carbon dioxide)

reported with programmes providing regular follow-up with home care interventions and patient education [4]. Multicentred randomized controlled studies with larger follow-up periods are needed to create generalized recommendations regarding HMV follow-up, specially focusing on the cost-effectiveness of the home care strategy.

Despite all the questions indicated above and with the technological advances in our society, the use of telemonitoring in the follow-up of HMV is a rational thought. Telemonitoring is a complex intervention that aims to deliver specialized healthcare remotely that includes the electronic transmission of patient information to the healthcare system and the follow-up response by the healthcare professional. As the use of NIV is increasing worldwide, with the significant costs associated with hospital admission and the difficulty in discharging the ventilator dependent patients, the use of telemonitoring is becoming an attractive option. Some advantages reported would be the possibility of easier contact between patients and healthcare team, less dislocation for patients/caregivers, continuous or more frequent monitoring of ventilation variables with immediately remote titration of ventilator parameters, possibility of earlier detection of clinical decompensation or other problems related to the ventilator [2, 4, 8].

Regarding home care, the protocols for the use of telemonitoring have been variable across published articles in the literature. Some authors have used different electronic devices and follow-up strategies using a combination of phone calls or video conference with different time ranges (weekly to 3 months), compliance data from the ventilator downloaded accordingly to a designed study protocol with remotely ventilator titration, punctual, nocturnal or continuous SpO2 monitoring or use of tele-spirometry/peek expiratory flow meter or other portable wearable devices that continuously measure a number of physiologic variables (SpO2, heart rate, electrocardiogram, among others) [2, 4]. Concerning cost-effectiveness, Vitacca et al. have demonstrated that tele-monitoring is cost-effective in more severe and frail patients, dependent of HMV and/or oxygen therapy mainly due to the prevented hospitalizations [11]. However, most studies are single centred with a small sample, with different inclusion and exclusion criteria and without cost-effectiveness evaluation, making it difficult to be confident about the role of telemonitoring in patients with CRF under HMV.

Telemedicine may be helpful not only as a part of the follow-up programmes but also to provide other services such as rehabilitation, social support and palliative or end-of-life care. Some authors have been reporting positive experiences in tele-rehabilitation using phone calls, videoconference, reinforcement messages, emails or websites, biological sensors able to send data or medical devices able to be programmed at distance, mainly in COPD patients [2]. Regarding palliative care, improvements in symptoms control and easier communication between patients/caregivers and the health professional have been stated; however, groups defend that telemedicine should be an additional tool and not a substitute for hospital or home visits [2, 12]. Most of this encouraging information arises from studies in non-ventilated patients; consequently, more studies are needed to extrapolate results to HMV.

Nevertheless, given the scarcity of standardized and controlled studies with cost-effectiveness evaluation and the inequality of access to these technologies across the globe, much more research must be done before considering telemedicine a key element in improving the management of HMV patients. Furthermore, there are other barriers that prevent the wider diffusion of telemedicine, such as lack of awareness and confidence in electronic solutions among patients and healthcare professionals, lack of interoperability between devices from different companies, lack of legal clarity for its usage/reimbursement and lack of transparency of utilization of data collected and regional differences [2, 8].

40.3 Conclusion Discussion

The management of patients receiving HMV requires the clinician to integrate clinical and respiratory physiological data as well as sleep assessment and knowledge of ventilator technol-

ogy. The recommended approach is to evaluate these patients regularly and in a multidisciplinary team. A combined approach of outpatient clinic, home care and telemonitoring may be a more suitable way to follow-up these patients; therefore, more multicentred, controlled trials with standardized protocols are needed to confirm this assumption.

Key Major Recommendations

- Chronic diseases, including home mechanical ventilated (HMV) patients, increase dramatically the burden on healthcare systems.
- Follow-up of HMV should be performed regularly by a multidisciplinary team to prevent hospitalizations.
- The range of lung function tests should be tailored to the individual patient, depending on the underlying disease and if there are any persistent symptoms or problems related to the ventilator.
- Home care and telemonitoring may be added as one of the services offered during the follow-up programme. However, more studies are needed to identify who are the ideal candidates, what variables should be measure, when and for how long should patients receive it.

References

1. Lloyd-Owen SJ, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005; https://doi.org/10.1183/09031936.05.00066704.
2. Ambrosino N, et al. Tele-monitoring of ventilator-dependent patients: a European Respiratory Society Statement. Eur Respir J. 2016;48(3):648–63. https://doi.org/10.1183/13993003.01721-2015.
3. Mineiro MA, Guimarães MJ, Winck JC. Organization of home mechanical ventilation in Portugal: characterization of current centers and a pathway to uniformization. Pulmonology. 2020;26:84–9.
4. Elliott M, Nava S, Schönhofer B. Non-invasive ventilation and weaning: principles and practice. Non-invasive ventilation and weaning: Principles and practice. Boca Raton: CRC Press; 2010. https://doi.org/10.1201/b13434.
5. Sauty A, Uldry C, Debétaz LF, Leuenberger P, Fitting JW. Differences in PO_2 and PCO_2 between arterial and arterialized earlobe samples. Eur Respir J. 1996;9:186–9.
6. Angelucci A, Aliverti A. Telemonitoring systems for respiratory patients: technological aspects. Pulmonology. 2020;26:221–32.
7. Dellacà RL, Gobbi A, Pastena M, Pedotti A, Celli B. Home monitoring of within-breath respiratory mechanics by a simple and automatic forced oscillation technique device. Physiol Measure. 2010; https://doi.org/10.1088/0967-3334/31/4/N01.
8. Duiverman ML. "Tricks and tips for home mechanical ventilation". Home mechanical ventilation: set-up and monitoring protocols. Pulmonology. 2020; https://doi.org/10.1016/j.pulmoe.2020.08.002.
9. Hazenberg A, Kerstjens HAM, Prins SCL, Vermeulen KM, Wijkstra PJ. Initiation of home mechanical ventilation at home: a randomised controlled trial of efficacy, feasibility and costs. Respir Med. 2014; https://doi.org/10.1016/j.rmed.2014.07.008.
10. Duiverman ML, et al. Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. Thorax. 2020; https://doi.org/10.1136/thoraxjnl-2019-213,303.
11. Vitacca M, et al. Tele-assistance in chronic respiratory failure patients: a randomised clinical trial. Eur Respir J. 2009;33(2):411–8. https://doi.org/10.1183/09031936.00005608.
12. Vitacca M, et al. Telemedicine to support end of life in severe chronic respiratory failure patients at home. J Med Person. 2009;7:85–90.

Part VI

Relationships between Noninvasive Ventilation and Lung Function Measurement. In Outcome and Quality-of-Life

Pulmonary Function Testing: Predictors and Readmissions

41

Angela Tadeo, Thomas D. Clevenger, and Bahman Saatian

Abstract

Hospital readmission is a key measure for quality of patient care in U.S. hospitals. Readmission not only takes a financial toll on the patient and the system, but it also becomes a burden on the patient's psychosocial wellbeing. Pulmonary diseases are among top conditions identified with the most readmissions. Pulmonary function testing has been considered as a tool to identify the patients that can safely be discharged from hospital.

Keywords

Pulmonary function test (PFT) · Suboptimal peak inspiratory flow (sPIF) · Chronic obstructive pulmonary disease (COPD) · Six-minute walk test (6MWT)

A. Tadeo · T. D. Clevenger
Department of Medicine, Pulmonary and Critical Care Section, Veteran Affairs Long Beach Healthcare System, Long Beach, CA, USA
e-mail: angela.tadeo@va.gov; thomas.clevenger@va.gov

B. Saatian (✉)
Department of Medicine, Pulmonary and Critical Care Section, Veteran Affairs Long Beach Healthcare System, Long Beach, CA, USA

Department of Medicine, UC Irvine, Irvine, CA, USA
e-mail: bsaatian@hs.uci.edu

Abbreviations

6MWT	6-minute walk test
ABG	Arterial blood gas
AHRQ	Agency for Healthcare Research and Quality
COPD	Chronic obstructive pulmonary disease
DLCO	Diffusion capacity for carbon monoxide
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
PFT	Pulmonary function test
PIF	Peak inspiratory flow

41.1 Introduction

Quality pulmonary function testing (PFT) can be a reliable component in diagnosing and screening patients to aid in directing care and determine risk for surgery. PFT can also be used to predict the likelihood of readmission.

According to the Healthcare Cost and Utilization Project by the Agency for Healthcare Research and Quality (AHRQ), hospital readmission rates are a key indicator for quality patient care in the United States and help identify potential savings [1, 2]. In 2016, the AHRQ determined

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_41

that the average overall all-cause readmission within 30 days cost was roughly 13% more compared to the initial admission cost. However, when broken down by principal diagnosis and looking into respiratory system diseases alone, the average 30-day readmission cost was 26% higher than initial admission cost. Therefore, employing readmission predictor data to mitigate patient decline post discharge could lead to cost effective medicine and improved patient wellness in the long term.

This chapter will discuss studies that have shown that initial and serial PFT, along with other discharge criteria, could predict potential decline and avoidable readmission.

In this chapter, we will discuss certain pulmonary function tests and how it could impact inpatient care as well as its usefulness in determining readiness for release from hospital. We will also discuss tests to be used to alert healthcare providers of any interventions needed to ensure successful discharge and manageable outpatient support.

41.2 Discussion and Analysis of the Main Topics

41.2.1 Pulmonary Function Testing

Pulmonary function testing, in conjunction with radiologic imaging and arterial blood gasses (ABG), affords healthcare providers a comprehensive look into patients' pulmonary health to aid in appraising dyspnea and disease management. PFTs also allow for objective risk assessment and alert clinicians of need for change or progression in treatment [3].

Basic PFT determine lung functionality by measuring volumes and capacities, air flow, diffusion rate, and respiratory muscle strength among other functions as well.

Simple spirometry measures vital capacity (VC) or the most air one can move in and out of one's lungs. FVC or forced vital capacity involves moving the most air in and out of lungs but with significant effort to empty out the lungs of air as quickly and as thoroughly as possible. This maneuver captures maximal air flow as well as VC. A comparison study by obtaining FVC before and after bronchodilator administration can assess airway hyperreactivity or unmask any latent reversible airway obstruction. FEV_1, or forced expiratory volume in the first second of exhalation, measures the volume of air expired in the first second when performing an FVC. FEV_1/FVC, or the expression of FEV_1 relative to FVC, shows the ratio of expired air in the first second in proportion to the total volume of air exhaled.

Other pulmonary function tests, such as measuring maximal inspiratory and expiratory pressures (MIPs and MEPs) which is used to assess respiratory muscle strength or a simple six-minute walk test (6MWT) which determines the point of maximal oxygen uptake [3], can also be used to ascertain patients' readiness for discharge. Referring to tests prior to admission, even unrelated to cause of admission, can be a useful source of information and should be utilized to complete the picture of the patient's health. Although the tests listed are not comprehensive, it gives us an idea of how PFTs can be one of the determining factors whether discharge is safe and signals risk for readmission.

41.2.2 Readmission Predictors

Once a patient is admitted, the collaborative goal of every discipline is to progress to discharge. Having all the necessary information to conclude that a patient is ready for discharge could better predict how a patient will fair post discharge.

Comorbidity measures such as the Charlson Comorbidity Index (CCI) and the Elixhauser Score, commonly used to for clinical prognosis, include chronic obstructive pulmonary disorder (COPD) as a category for scoring. Comorbidity measures condense comorbidity data into clear and useful metrics rather than trying to appraise each comorbidity independently [4]. Using PFT to determine COPD diagnosis contributes to readmission indices scoring such as LACE (length of stay, acuity on admission, comorbidity and emergency department visits) or PARR (Patient at Risk of Hospital Readmission). PFT

obtained prior to admission, whether planned or unplanned, can, therefore, be used to quantify risk of readmission as well as identifying any underlying cause of complications that could be prevented.

When assessing patients for impending discharge and taking into consideration an accumulation of recent PFTs, we see that with just simple spirometry, health care providers can obtain reasonable insight into a patient's pace and course of recovery. Even referring to a single recent PFT can alert a prescribing provider if certain means of taking medication, for example, DPI vs. nebulizer, is appropriate according to the patient's ability to generate enough inspiratory force.

A study conducted between May 2014 and December 2015 by the Wake Forest School of Medicine Medical Center in North Carolina found that patients with peak inspiratory flow (PIF) of less than 60 L/min were considered suboptimal (sPIF) and had higher rates of 90-day readmission for COPD, days to all-cause readmissions [5]. PIF is derived from the inspiratory curve of a flow volume loop. sPIF is common during an acute COPD exacerbation (AECOPD). This study showed that patients discharged with nebulizers compared to DPIs (dry powder inhalers) have a significantly lower rate of all-cause and COPD 30- and 90-day readmission. DPI delivery is dependent on PIF, and, therefore, patients with sPIF would benefit from using a nebulizer, if available, as a means of delivering inhaled medication. Nebulized treatments do not require the patient to generate a higher than normal inspiratory flow and would only require tidal breathing for the treatment to be effective.

COPD patients that are seen in the emergency department (ED) who have a post-bronchodilator FEV1 of 40% and below should have more aggressive treatment or consider hospital admission. Patients with an FEV_1/FVC ratio of 46.4 ± 15.2 have a higher frequency of readmission. A lower FEV_1 along with a dyspnea score of 3 or higher should be flagged for an increased risk hospital readmission [6]. A lower FEV_1 has been associated with an increased risk of hospitalization [7] as well as readmission, and some studies identified patients with an FEV_1 of 40% and below of predicted normal to be at risk of rehospitalization [8, 9].

Patients admitted for rib fractures could benefit from daily FVCs to monitor for any signs of deterioration. A study conducted by the Department of Surgery in West Virginia University in 2018 concluded that patients whose FVC declined to less than 1 L during admission are at high risk for pulmonary complications [10]. Even without decompensation, increased intervention, such as initiation of incentive spirometry (IS) and positive expiratory pressure (PEP) therapy, should be considered to prevent further deterioration. It is also recommended that daily FVCs be performed on patients with rib fractures with FVCs over 1 L. If an FVC measurement falls 25% from baseline, then PEP and IS should be increased in frequency and consider pain consult [10].

Pulmonary function tests, such as cardiopulmonary exercise test (CPET), spirometry, and carbon monoxide diffusion capacity of the lung (DLCO), are commonly used to assess preoperative risk. Based on a study published in the *Japanese Association of Thoracic Surgery*, preoperative FEV_1 and DLCO are used to calculate a postoperative predicted (ppo) FEV_1 and DLCO for lung surgery patients. Patients with a ppoFEV_1 and ppoDLCO of ≥60% are low risk [11]. Complemented with the 6-minute walk test (6MWT), oxygen desaturation is also a good predictor for surgery outcome [12].

Cystic fibrosis patients are regularly monitored through PFT and, therefore, have a well-documented spirometry trend. Patients admitted to the hospital for acute pulmonary exacerbation will be closely followed to alert healthcare givers of any early signs of deterioration and to evaluate for discharge. A study by Krivchenia et al. aimed to determine optimal length of stay by initiating spirometry early into the hospitalization to detect improvement and plateauing of FEV_1. The study suggests that a quick rebound early into hospitalization could be attributed to poor compliance at home. The typical course of treatment in hospital addresses decrease in FEV_1 due to mucus plugging brought on by compliance issues, and a pla-

teau in FEV_1 is noted around day eight of hospitalization. By early detection of stabilization of in-hospital peak FEV_1, length of stay could be shortened in a safe and cost effective manner [13]. Discharging patients close to pre-exacerbation baseline with documented stabilization could likely prevent readmissions by offering clinicians an objective perspective on a patient's measurable outcome and steady progress.

41.3 Conclusion Discussion

Hospital readmission is considered as a key measure for the quality of patient care in U.S. hospitals. Pulmonary diseases such as pneumonia and COPD are among the top ten conditions identified with the most readmissions. A literature review revealed scant number of publications that investigated the role of pulmonary function testing as a predictor of hospital readmission for pulmonary conditions. One of the limitations to use pulmonary function testing in acutely hospitalized patient is the inability to optimally perform the test. With objective, absolute, and reliable data, derived from quantifying mechanisms such as pulmonary function testing, healthcare givers can justifiably extend the stay or safely discharge patients with some confidence by confirming or analyzing incongruous symptoms. Based on current evidence, we recommend using pulmonary function testing, measuring post-bronchodilator FEV1, peak inspiratory flow (PIF), and performing exercise oximetry to assess the readiness of patients for discharge and to predict the risk of hospital readmission.

Key Major Recommendations

- Pulmonary function testing with FEV1/FCV ratio.
- Pre- and post-bronchodilator FEV1 and FVC.
- Peak inspiratory flow (PIF) measurement.
- Exercise oximetry prior to discharge.
- Maximal inspiratory and expiratory pressure (MIPs and MEPs) measurement to assess respiratory muscle strength.

References

1. Bailey MK, Weiss AJ, Barrett ML, et al. Characteristics of 30-Day all-cause hospital readmissions, 2010–2016: statistical brief #248. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs, Agency for Healthcare Research and Quality (US) 2019, p. 1.
2. Hines AL, Barrett ML, Jiang HJ, et al. Conditions with the largest number of adult hospital readmissions by payer, 2011. Statistical brief #172. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs 2014, p. 1.
3. Miaskiewicz JJ. Pulmonary function testing. In: McKean SC, et al., editors. Principles and practice of hospital medicine. 2nd ed. McGraw-Hill; 2017. Chapter 110.
4. Loh CH, Peters SP, Lovings TM, et al. Suboptimal inspiratory flow rates are associated with chronic obstructive pulmonary disease and all-cause readmissions. Ann Am Thorac Soc. 2017;14(8):1305–11.
5. Austin SR, Wong YN, Uzzo RG, et al. Why summary comorbidity measures such as the Charlson Comorbidity Index and Elixhauser Score work. Med Care. 2015;53(9):65–72.
6. Cerezo Lajas A, Gutiérrez González E, Llorente Parrado C, et al. Readmission due to exacerbation of COPD: associated factors. Lung. 2018;196(2):185–93.
7. Vestbo J, Rasmussen FV. Respiratory symptoms and FEV1 as predictors of hospitalization and medication in the following 12 years due to respiratory disease. Eur Respir J. 1989;2(8):710–5.
8. Emerman CL, Effron D, Lukens TW. Spirometric criteria for hospital admission of patients with acute exacerbation of COPD. Chest. 1991;99(3):595–9.
9. Gaude GS, Rajesh BP, Chaudhury A, et al. Outcomes associated with acute exacerbations of chronic obstructive pulmonary disorder requiring hospitalization. Lung India. 2015;32(5):465–72.
10. Warner R, Knollinger P, Hobbs G, et al. Forced vital capacity less than 1: a mark for high-risk patients. J Trauma Acute Care Surg. 2018;85(2):271–4.
11. Sawabata N, Nagayasu T, Kadota Y, et al. Risk assessment of lung resection for lung cancer according to pulmonary function: republication of systematic review and proposals by guideline committee of the Japanese Association for Chest Surgery 2014. General Thorac Cardiovasc Surg. 2015;63(1):14–21.
12. Nakagawa T, Tomioka Y, Toyazaki T, et al. Association between values of preoperative 6-min walk test and surgical outcomes in lung cancer patients with decreased predicted postoperative pulmonary function. General Thorac Cardiovasc Surg. 2018;66(4):220–4.
13. Krivchenia K, Tumin D, Nemastil CJ, et al. Timing of spirometry may impact hospital length of stay for cystic fibrosis pulmonary exacerbation. Lung. 2018;196(2):207–11.

The Effect of Intensive Care on Quality of Life

42

İlhan Bahar and Antonio M. Esquinas

Abstract

When treating and intervening in intensive care units, mortality effect is generally taken into consideration. The quality of life the patient will have in intensive care and afterwards is not considered. Patients' quality of life is also important. Some people may prefer a quality life to mortality.

Keywords

Quality · Life · Intensive care

Abbreviations

EQ-5D	EuroQOL Five Dimensions Questionnaire
EQ-5D-3L	EuroQOL Five Dimensions Questionnaire 3-Level Version
EQ-VAS	The EuroQol Visual Analogue Scale
SF-12	The 12-Item Short Form Health Survey
SF-36	The 36-Item Short Form Survey

İ. Bahar (✉)
Anesthesiology and Reanimation Department, Çiğli Education and Research Hospital, İzmir, Turkey

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

42.1 Introduction

Health-related quality of life is measured on admission to the intensive care unit. Patients, their relatives, physicians, and nurses want to know about the effects of long-term intensive care stay on physiological and psychological factors [1].

Quality of life has several components. Ability in different roles such as physical activities and fulfilling beliefs, the degree and quality of social interaction, psychological well-being, happiness, life situations, and life satisfaction are listed amongst these. It also reflects life experiences, important life events, and the current stage of life, and in this regard, factors that define quality of life also include gender, socioeconomic status, age, and generation [2].

It covers the individual's point of view and is evaluated through the eyes of the relative.

42.2 Discussion and Analysis of Main Topics

42.2.1 Measurement Methods

There are three types of health-related quality of life measurement instruments: disease-independent generic, disease-specific, and complaint or domain-specific. Generally, generic and disease-specific ones are preferred.

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_42

As a result of the 2002 Expert Consensus Roundtable Conference, they propose two The 36-Item Short Form Survey (SF-36), and EuroQOL five dimensions questionnaire (EQ-5D) measurement methods [3]. The measurement methods frequently preferred in intensive care units are generic and are less sensitive to specific conditions, in general [4]. SF-36 includes 36 questions that examine patients from eight different angles: physical function, social function, social function, role limitation based on physical problem, role limitation due to emotional problem, general mental problems, energy/vitality, body pain, and general health perception. The shorter version of SFf-36, the 12-Item Short Form Health Survey (SF-12), is an easy and feasible form of measurement and can also reduce intensive care costs [5]. However, it may have a lower power to predict the result than p-36. SF-12 provides information about physical health summary score and mental health summary score [6].

Another survey that is not specific for any disease was developed by the EuroQol group in 1990. However, it can predict an outcome regarding the overall health, and it is easy to use. It has been translated into 171 languages. The EQ-5D questionnaire has two components: health state description and evaluation. The 5D part is about general health and tries to define it from five aspects: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the evaluation part, the respondents evaluate their overall health status using (SF-12), The EuroQol Visual Analogue Scale (EQ-VAS) [7].

Can instruments guide the applications and treatments for intensive care patients?

Healthcare professionals may want to know the quality of life of patients hospitalized in intensive care with acute illness before intensive care admission. It is necessary to inform the patients correctly whether the treatment of the patient will be continued or not [8]. Previous studies have shown that poor quality of life before admission to intensive care is seriously associated with the prognosis in terms of survival and leads to impairment in quality of life after discharge [9]. The effects of treatments and applications performed in intensive care units on mortality and morbidity are generally taken into consideration. Whereas, the effect of the treatment or application on the quality of life of the patient is not considered, in general. In their future life, some people find it important to be able to do their daily work or pain-free life. Patients do not want to experience any situations that are described as worse than death. These situations include urinary or bowel incontinence, to be dependent on a mechanical ventilator, being unable to get out of bed, not being able to eat, and persistent cognitive impairment. Quality is also important in the concept of life expectancy. The measurements can provide information about the necessary interventions to improve the quality life.

42.2.2 Use of Instruments in Intensive Care Conditions

The instruments can predict the quality of life of intensive care patients in the short, middle, and long terms. In a study conducted in an intensive care unit, the mental score of quality of life was found to be low, and the score was improved significantly following 8–26 weeks of discharge [10]. In the study of Feemster et al., the patients were followed for 2 years and the quality of life score of patients was found to be lower compared to the pre-hospitalization score. Both scores may not provide sufficient information about intensive care-related quality of life [11]. Evidence on the power of instruments to predict the quality of life of patients in intensive care is not yet sufficient.

The relatives of the patients usually answer measurement questions about the life quality expectancy [12]. Therefore, the studies performed on this subject may not yield completely matching results in terms of expectancy of patients and their relatives.

Determining the quality of life for someone else requires empathy, to imagine what it feels like to be that person, and speculate about the impact of healthcare on their life experiences.

The literature on the agreement between patients and their relatives on the assessment of quality of life expectancy before admission to the ICU is not very precise. However, the relatives of patients are important for information about the future life of the patients.

42.3 Conclusion Discussion

The patient's quality of life is as important as mortality in intensive care treatments and applications. The instruments can guide the treatments and applications in intensive care. There is a need for future, randomized large-scale studies on this subject.

Key Major Recommendations

- When treating patients in intensive care, the life expectancy of patients should be considered.
- More reliable scales should be developed.

References

1. Wu A, Gao F. Long-term outcomes in survivors from critical illness. Anaesthesia. 2004;59:1049–52.
2. Sevinc S, Akyol AD. Cardiac risk factors and quality of life in patients with coronary artery disease. J Clin Nurs. 2010;19:1315–25.
3. Angus DC, Carlet J, On behalf of the 2002 Brussels Roundtable Participants. Surviving Intensive Care: a report from the 2002 Brussels Roundtable. Intensive Care Med. 2003;29:368–77.
4. Vainiola T, Roine RP, Pettilä V, et al. Effect of health-related quality-of-life instrument and quality-adjusted life year calculation method on the number of life years gained in the critical care setting. Value Health. 2011;14:1130–4.
5. Ware JE, Kosinski M, Keller SD. A 12-Item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220–33.
6. Hofhuis JG, Spronk PE, van Stel HF, et al. Quality of life before intensive care unit admission is a predictor of survival. Crit Care. 2007;11:R78.
7. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199–208.
8. Tereran NP, Zanei SSV, Whitaker IY. Quality of life before admission to the intensive care unit. Rev Bras Ter Intensiva. 2012;24:341.
9. McKinley S, Aitken LM, Alison JA, et al. Sleep and other factors associated with mental health and psychological distress after intensive care for critical illness. Intens Care Med. 2012;38:627–33.
10. Feemster LC, Cooke CR, Rubenfeld GD, et al. The influence of hospitalization or intensive care unit admission on declines in health-related quality of life. Ann Am Thorac Soc. 2015;12:35–45.
11. Hofhuis JGM, van Stel HF, Schrijvers AJP, Rommes JH, Spronk PE. ICU survivors show no decline in health-related quality of life after 5 years. Intensive Care Med. 2015;41:495–504.
12. Hofhuis J, Hautvast JLA, Schrijvers AJP, et al. Quality of life on admission to the intensive care: can we query the relatives? Intensive Care Med. 2003;29:974–9.

Quality of Life in Chronic Obstructive Pulmonary Diseases

43

Bruno Cabrita, Gil Gonçalves, André Cabrita, and Sara Dias

Abstract

Health-related quality of life defines the quality of life associated with health status, disease, and its treatment. In the last decades, there has been an increasing number of people living with chronic respiratory diseases and severe symptoms that limit daily life activities. An improvement in quality of life can be assessed by questionnaires and should be a primary treatment outcome.

Keywords

Health · Quality · Symptoms · Disease · Chronic

B. Cabrita (✉) · S. Dias
Pulmonology Department at Hospital Pedro Hispano, Matosinhos, Portugal

G. Gonçalves
Pulmonology Department at Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

A. Cabrita
Cardiology Department at Centro Hospitalar Universitário São João, Porto, Portugal

Abbreviations

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AQLQ	Asthma Quality of Life Questionnaire
CAT	COPD Assessment Test
CCQ	COPD Control Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Questionnaire
CRQ-SAS	Chronic Respiratory Questionnaire Self-Administered Standardized Format
FEV1	Forced expiratory volume in 1 second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-Related Quality of Life
mMRC	Modified Medical Research Council
NCF	Non-cystic fibrosis
QOL-B	Quality of Life Questionnaire-Bronchiectasis
SGRQ	St. George's Respiratory Questionnaire
SMAS-30	Self-Management Ability Scale 30
SRIQ	Severe Respiratory Insufficiency Questionnaire
WHO	World Health Organization

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_43

43.1 Introduction

43.1.1 What Is Health-Related Quality of Life?

Health-related quality of life (HRQoL) is a complex broad concept that defines the quality of life associated with health status, disease, and its treatment. It includes a comprehensive assessment of physical, social, and psychological burden of patients' diseases and disabilities [1, 2]. It also represents the patients' perception of their current level of functioning and status in life compared with their belief of ideal condition, influenced by their culture, value systems, goals, and expectations. It is described in relation with patients' previous life experiences, gender, socioeconomic status, age, and generation [2]. According to the World Health Organization (WHO), health does not simply represent the absence of disease, but also a complete state of well-being, regarding psychical, mental, and social conditions [2].

With the significant improvement of healthcare in the last decades, there has been an increasing number of people living with chronic diseases, including chronic pulmonary obstructive diseases with severe symptoms that limit daily life activities [2, 3]. Chronic obstructive lung diseases, like chronic obstructive pulmonary disease (COPD), asthma and bronchiectasis are usually slowly progressive, and require progressively more treatment and healthcare assistance and costs. These conditions contribute to overall worsen of quality of life, limiting daily routines and productivity [2]. Besides symptoms, chronic lung diseases often present with other comorbidities, including depression and anxiety disorders, that also have an impact in symptoms and disease burden, affects quality of life, and should be regularly evaluated in consultation [1].

HRQoL is an indicator of overall health and its improvement should, therefore, be a primary treatment outcome and a determinant of therapeutic benefits, whether in hospital or primary care setting [2]. It can be assessed by self-questionnaires or interview and some specific tools are described and validated in the literature. They consist in multiple questions of self-perceived health condition, including physical and emotional well-being. There is an increasing necessity to aim, not only, to treat for the restoration of health status, but also the restoration of HRQoL as well to, at least, acceptable levels [3]. Ideal assessment tools must have reliability, content validity, sensitivity to changes, and responsiveness in order to evaluate clinical evolution over time. They also need to be simple and practical to use in clinical day practice [2].

43.2 Discussion and Analysis of Main Topics

43.2.1 How Is the Quality of Life in Patients with Chronic Obstructive Pulmonary Disease?

COPD represents one of the major causes of morbidity and mortality worldwide [1, 4, 5]. It is characterized by persistent and progressive airflow limitation and chronic respiratory symptoms with significant negative impact in daily-life activities [3, 6]. Symptoms include dyspnea, cough, fatigue, and skeletal muscle dysfunction when the disease progresses over time. COPD symptoms in men may differ from women. Women tend to have more dyspnea and higher prevalence of depression and anxiety, with direct relation with HRQoL [1].

Lung function is characteristically impaired in patients with COPD. Forced expiratory volume in 1 second (FEV1) is decreased but has a poor correlation with symptoms and HRQoL [6]. Patients who have moderate to severe COPD (FEV1 30–79% of predicted value) have more exacerbations and higher risk of hospital admissions with progressive worsening of lung function and disease severity, compared with patients with less severity of the disease (FEV1 $\geq$ 80% of predicted value). Thus, exacerbations of COPD are related with worse HRQoL in these patients [7, 8].

COPD may also have severe compromise of normal ventilation and patients may present with

respiratory failure. These have worse survival and an estimated 5-year mortality of 70–100% [5].

COPD often coexists with other comorbidities with direct impact in physical and emotional well-being [1, 6]. These risk factors, like smoking, the major risk factor for the development of COPD, contribute to the development of other diseases that often coexist in the same patient, increasing the morbidity and mortality. These include cardiovascular diseases, musculoskeletal impairment, diabetes mellitus, depression, among others. In these patients, health status is compromised, the need for more medication and the risk of hospitalization increases, contributing to higher healthcare related costs [8].

COPD pharmacological and non-pharmacological treatments are crucial for symptom control and have significant impact in HRQoL [5]. Pharmacological treatments include inhalers with bronchodilators (anti-muscarinic and β-agonist agents), sometimes inhaled corticosteroids. Non-pharmacological treatments include vaccination (influenza and anti-pneumococcal), smoking cessation, pulmonary rehabilitation, and adoption of a healthy lifestyle [8]. Self-management approaches are very important and include written action plans that aim to help and teach patients to recognize and manage early signs of exacerbations, reducing the need for hospitalization care. Studies beyond the use of this self-management strategy and the association with HRQoL still lack in the literature [4].

43.2.2 Which Tools Are Available to Measure Quality of Life of Patients with COPD?

Global Initiative for Chronic Obstructive Lung Disease (GOLD): GOLD categorizes COPD patients according to the severity of airway obstruction, using post-bronchodilator FEV1. GOLD 1 is mild obstruction with FEV1 ≥ 80% of predicted, GOLD 2 is moderate obstruction with FEV1 50–79% of predicted, GOLD 3 is severe obstruction with FEV1 30–49% of predicted, and GOLD 4 is very severe obstruction with FEV1 < 30% of predicted [4, 8].

Table 43.1 Modified Medical Research Council (mMRC) for dyspnea scale

Modified Medical Research Council
mMRC Grade 0: Dyspnea only with strenuous exercise
mMRC Grade 1: Dyspnea when hurrying on the level or walking up a slight hill
mMRC Grade 2: Dyspnea when walking at own pace on the level
mMRC Grade 3: Dyspnea when walking 100 m on the level
mMRC Grade 4: Dyspnea when dressing/undressing

Used with the permission of the Medical Research Council. Adapted from [11]

Modified Medical Research Council (mMRC): mMRC represents a five-item scale for measuring dyspnea in daily life activities and disease burden in COPD patients (Table 43.1) [4]. It is related with health status and also helps predicting mortality risk [8].

COPD Assessment Test (CAT): CAT is an eight-item tool used to measure symptoms and health status impairment in COPD patients [8].

Self-Management Ability Scale 30 (SMAS-30): SMAS-30 is a valid and reliable tool to measure self-management in chronic diseases, including physical and social well-being. This score is independently associated with HRQoL in COPD patients [4].

Chronic Respiratory Questionnaire Self-Administered Standardized Format (CRQ-SAS): CRQ-SAS is a validated questionnaire with 1–7-point scale that measures health status of patients with COPD [4].

Chronic Respiratory Questionnaire (CRQ) and St. George's Respiratory Questionnaire (SGRQ): These are comprehensive assessments of symptoms in COPD, although too complex for routine use in clinical practice [8].

COPD Control Questionnaire (CCQ): CCQ represents a suitable and simple assessment tool in COPD patients, with a 10-item scale, used to assess HRQoL in patients with COPD [8].

Severe Respiratory Insufficiency Questionnaire (SRIQ): SRIQ is considered the most extensive measure for HRQoL in patients with COPD and hypercapnic chronic respiratory failure [5].

43.2.3 How Is the Quality of Life in Patients with Asthma?

Asthma is a chronic respiratory disease that may present with severe symptoms with significant limitations on daily life activities [3, 9]. It is characterized by chronic inflammation and hyperresponsiveness of the airways and patients refer wheeze, dyspnea, chest tightness, and nonproductive cough. Typically, these symptoms and airflow limitation vary over time and in intensity, allowing the diagnosis. Patients frequently have worse symptoms at night, with exposure to cold air, allergens, and with physical exercise. In severe cases, the airflow may become persistent, especially when there is a history of smoking habits or uncontrolled disease [10]. The control of the disease depends of the management of symptoms, medication, and reducing the risk of future exacerbations and adverse outcomes, although these may not be completely related [10].

Asthma severity is assessed by the required level of therapeutic to control symptoms and exacerbations [10]. It is estimated that 5–10% of patients with asthma have a severe uncontrolled condition, despite optimal medical treatment, with great impact in HRQoL [9]. These patients experience great limitation in daily life activities and a heavy burden related with severe symptoms, exacerbations, sleep disorders, prescriptions, and their side-effects, particularly systemic corticosteroids often prescribed in severe cases. Corticosteroids increase the risk of adverse effects and morbidity of patients with asthma, including obesity, osteoporosis, cataracts, diabetes mellitus, hypertension, increased risk of infections, depression, and anxiety disorders. Also, these patients are limited in their social life and interactions, work capacity, and emotional and mental health. Patients with severe asthma have a significant economic burden related with the chronic prescriptions and medical care required, but also due to the conflict with their professional activities that often contribute to worsening of their symptoms and require changing or suspension of the activity [10].

There is a relation between symptoms severity, especially chest tightness and dyspnea, exacerbations, specific asthma triggers, and impaired HRQoL. Regarding this matter, the most important clinical parameters are the disease severity, including spirometry values, hospitalization due to exacerbations, and also the participation on social activities [9].

Patients with asthma commonly present with other comorbidities that have a direct impact in symptoms and HRQoL, including depression and anxiety disorders, sleep disturbances, gastroesophageal reflux, and obesity [9].

43.2.4 Which Tools Are Available to Measure Quality of Life of Patients with Asthma?

Asthma Control Test (ACT): ACT includes four symptom/reliever questions and also a self-assessment level of control (Table 43.2) [10].

Table 43.2 Asthma Control Test (ACT) questionnaire and possible answers

Asthma Control Test
In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?
All the time; most of the time; some of the time; a little of the time; none of the time
During the past 4 weeks, how often have you had shortness of breath?
More than once/day; once/day; 3–6 times/week; 1–2 time(s)/week; not at all
During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night or earlier than usual in the morning?
≥4 nights/week; 2–3 nights/week; once/week; once or twice; not at all
During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?
≥3 times/day; 1–2 time(s)/day; 2–3 times/week; ≤once/week; not at all
How would you rate your asthma control during the past 4 weeks?
Not controlled at all; poorly controlled; somewhat controlled; well controlled; completely controlled

Asthma Control Questionnaire (ACQ): ACQ represents a tool to assess symptoms, reliever use, and FEV1 values. The score is calculated as the average value of all responses [10].

Asthma Quality of Life Questionnaire (AQLQ): AQLQ assesses activity limitations, symptoms, emotional functioning, and environmental stimuli in patients with asthma [9].

43.2.5 How Is the Quality of Life in Patients with Bronchiectasis?

Bronchiectasis represents a chronic pulmonary disease characterized by an abnormal persistent dilatation and distortion of bronchi, with destruction of the airway wall [1]. This promotes difficulties in the clearance of the airways with bacterial colonization, recurrent respiratory infections with prolonged use of antibiotics, hospitalization, and also progressive loss of lung function [1, 11]. Patients usually have chronic cough and sputum production, may be limited in daily life activities, and have impaired HRQoL [11, 12].

Non-cystic fibrosis (NCF) bronchiectasis treatment choices are limited due to lack of studies with validated clinical trial endpoints. In studies with patients treated with colistin versus placebo, a decrease in bacterial density of the airways was observed; however, there were no improvements in symptoms or lung function (FEV1), although an improvement in SGRQ was reported. Treatment endpoints should also focus on the improvement of symptoms and HRQoL, in order to develop new treatment strategies [12].

Bronchiectasis are often associated with COPD and both can significantly impair symptom control and HRQoL. Thus, bronchiectasis represents a predictive factor for poor quality of life in patients with COPD [1].

43.2.6 Which Tools Are Available to Measure Quality of Life of Patients with Bronchiectasis?

Quality of Life Questionnaire-Bronchiectasis (QOL-B): QOL-B is a valid and reliable tool developed to assess symptoms, physical and emotional functioning, treatment burden, and HRQoL in patients with NCF bronchiectasis [12].

SGRQ and Leicester Cough Questionnaire: These are tools designed to assess patients with COPD and patients with cough, respectively, that may be used for bronchiectasis patients [11].

43.2.7 Which Factors Influence Quality of Life in Chronic Pulmonary Diseases?

Disease and symptom control: An optimized medical therapy helps controlling patients' symptoms and the respiratory condition. In clinical day practice, some patients have problems with adherence to therapy, especially when their symptoms are mild. It is crucial that patients with chronic respiratory conditions adhere to their treatment in order to maintain control of their disease and preserve or improve HRQoL [9].

Health risk behaviors: Smoking habits are a well-known risk factor for chronic obstructive respiratory diseases. Drinking habits, obesity, and physical inactivity are all associated with worse HRQoL in chronic respiratory patients, and contribute to higher morbidity and mortality [2].

Comorbidities: The presence of multiple comorbidities, often present in chronic respiratory patients, include cardiovascular diseases, depression and anxiety disorders, or musculoskeletal disease, contribute to worse HRQoL [2, 8]. As previously explained, some respiratory diseases may coexist in the same patients (for example, COPD and bronchiectasis) and aggravate clinical evolution and outcomes [1].

Heart diseases: Patients with chronic respiratory diseases often have comorbidities, especially cardiovascular diseases. Heart diseases may present with several symptoms, like dyspnea, cough and chest tightness, that limit daily life activities, physical exercise, and contribute to worsen quality of life [2, 8]. Also, the exacerbation of one disease may precipitate the exacerbation of another.

Insomnia: Insomnia represents a common sleep disturbance of patients with chronic respi-

ratory diseases. It is responsible for a decline in health status, physical and psychological well-being, worse HRQoL, and increased mortality [2].

Disease perception: Studies refer that patients with a positive perception of the disease and belief that its impact on daily-life activities is less serious tend to have better HRQoL [6].

Culture: Studies report the influence of different cultural beliefs in HRQoL. Disease perception may differ among individuals and, consequently, HRQoL as well [2].

Positive affections: Positive affections influence HRQoL in chronic patients, improve mental health, and ability to cope with distress events and self-management [4].

Mindfulness: Mindfulness has reported benefits in pain-related symptoms and catastrophizing, decreasing negative thinking, and improving self-efficacy [4].

43.2.8 How to Improve Quality of Life in Patients with Chronic Respiratory Diseases?

Chronic obstructive respiratory diseases have significant impairment in HRQoL, morbidity, and mortality of patients. The best treatment available often requires chronic medication, including inhalers with bronchodilators, systemic corticosteroids in uncontrolled disease, and antibiotics. Severe disease management also includes treatment with long-term oxygen therapy and sometimes noninvasive ventilation when the patient has chronic respiratory failure. Healthcare need is part of the natural course of progressing diseases, especially when the risk factors persist, involving healthcare appointments, regular noninvasive and sometimes invasive diagnostic procedures, and hospital admissions due to exacerbations. Healthcare professionals are aware of these risks and outcomes and must provide patients the opportunity to improve their health literacy in their consultations. A well-informed patient who is provided with optimal medical therapy and written action plan to recognize early signs of worsening are key elements for promoting self-management and achieving success in the control of the disease and improved HRQoL [4].

Adherence to therapy may represent a challenge in clinical day practice. It has a major relevance in the control of the disease and, hence, disease outcomes and HRQoL. To improve adherence, it is important to educate patients about the disease, the purpose and timing to use their inhalers, and how to use them. Currently, there are many available choices in the market and each device has specific steps and small differences. Physicians must always try to adjust and simplify therapeutic regimens, especially in older patients with polymedication where the risk of confusion and mistakes are greater [9]. In the consultations, healthcare professionals need to find the time to review, correct errors, explain, and demonstrate the correct use of patients' inhalers.

Although not formally tested, the reduction of exacerbations in respiratory patients may improve well-being and HRQoL. Thus, the recognition of patients with higher risk of exacerbations may influence treatment approach and reduce morbidity and mortality, especially in patients with COPD [7].

Patients should be encouraged to improve their self-management skills and adopt a healthy lifestyle, including social activities, practice physical exercise or enroll in a pulmonary rehabilitation program to help control symptoms and cardiovascular risk factors, adopt a balanced diet, and quit drinking and smoking habits [2, 9].

For severely ill patients that remain symptomatic despite optimal bronchodilator therapy and non-medical treatment strategies, palliative care may be considered and have increasing importance in the management of severe cases. It provides life-enhancing approaches, focusing primarily on the treatment of symptoms and aiming to improve HRQoL, despite the expected course of the disease [2].

43.3 Conclusion

HRQoL is a complex concept that defines the quality of life associated with health status. Since the increasing number of people living with chronic obstructive lung diseases with severe symptoms limiting daily life activities, it has become of major importance the improvement in

HRQoL. It should be a primary outcome for medical interventions and should be more frequently assessed in consultations. In the available literature there are specific questionnaires to help physicians assess the quality of life of patients that might also be a helpful tool to guide and adjust treatment strategy.

Chronic obstructive pulmonary diseases include COPD, asthma, and bronchiectasis. These conditions may coexist in the same patient and also with other important comorbidities that share the same risk factors, like cardiovascular diseases, obesity, diabetes mellitus, depression and anxiety disorders, and sleep disturbances. These factors contribute to increased morbidity and mortality in these patients. Also, the control of the respiratory conditions depends on optimal medical and non-medical treatments, in patients often polymedicated, and so therapeutic adherence is often challenging.

Healthcare professionals need to promote health literacy among their patients, explain the natural course, characteristics and treatment of their respiratory conditions, give them written action plans, and promote self-management. These strategies help optimizing disease control, clinical evolution, and decreasing healthcare needs and costs, thus, promoting HRQoL despite patients' chronic conditions.

Key Major Recommendations

- HRQoL is a complex concept that defines the quality of life associated with health status.
- There is an increasing number of people living with chronic obstructive lung diseases with severe symptoms limiting daily life activities.
- The improvement in patients' HRQoL should be a primary outcome for medical interventions.
- HRQoL should be more frequently assessed in consultations.
- HRQoL may be assessed with specific tools and questionnaires validated in the literature.

References

1. Ekici A, Bulcun E, Karakoc T, Senturk E, Ekici M. Factors associated with quality of life in subjects with stable COPD. Respir Care. 2015;60(11):1585–91.
2. Megari K. Quality of life in chronic disease patients. Health Psychol Res. 2013;1:e27.
3. Cappa V, Marcon A, Gennaro G, Chamitava L, Cazzoletti L, Bombieri C, et al. Health-related quality of life varies in different respiratory disorders: a multi-case control population based study. BMC Pulmonary Med. 2019;19:32.
4. Benzo R, Abascal-Bolado B, Dulohery M. Self-management and quality of life in chronic obstructive pulmonary disease (COPD): the mediating effects of positive affect. Patient Educ Counsel. 2016;99:617–23.
5. Duiverman M, Wempe J, Bladder G, Kerstjens H, Wijkstra P. Health-related quality of life in COPD patients with chronic respiratory failure. Eur Respir J. 2008;32:379–86.
6. Weldam S, Lammers J, Heijmans M, Schuurmans M. Perceived quality of life in chronic obstructive pulmonary disease patients: a cross-sectional study in primary care on the role of illness perceptions. BMC Family Pract. 2014;15:140.
7. Seemungal T, Donaldson G, Paul E, Bestall J, Jeffries D, Wedzicha J. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157:1418–22.
8. GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD 2020), 2020. Available from https://gold-coped.org/.
9. Hossny E, Caraballo L, Casale T, El-Gamal Y, Rosenwasser L. Severe asthma and quality of life. World Allergy Org J. 2017;10:28.
10. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org.
11. Magge A, Ashraf S, Quitnner A, Metersky M. Quality of life in patients with bronchiectasis: a 2-year longitudinal study. Ann Transl Med. 2019;7(14):334.
12. Quittner A, O'Donnell A, Salathe M, Lewis S, Li X, Montgomery A, et al. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax. 2015;70:12–20.

Quality of Life in Neuromuscular Disorders

44

Gilda Cinnella, Guido Gambetti, and Michela Rauseo

Abstract

Neuromuscular disorders (NMDs) are a heterogeneous group of diseases causing progressive muscular impairment, which can even evolve into respiratory failure. Mechanical ventilation, mostly noninvasive ventilation (NIV), can often be necessary. In this chapter we will review the role of NIV in NMDs and how it could contribute to improve survival and quality of life (QoL), especially when timely employed.

Keywords

Neuromuscular disorders · Respiratory failure · Noninvasive ventilation · Quality of life

Abbreviations

AHI	Apnea/hypopnea index
ALS	Amyotrophic lateral sclerosis
BiPAP	Bilevel positive airway pressure
cmH_2O	Centimeters of water
CO_2	Carbon dioxide
DMD	Duchenne muscular dystrophy
FVC	Forced vital capacity
HRQOL	Health-related quality of life
INQoL	Individualized Neuromuscular Quality of Life Questionnaire
iVAPS	Intelligent volume-assured pressure support
MEP	Maximum expiratory pressure
MIP	Maximal inspiratory pressure
NIV	Noninvasive ventilation
NMDs	Neuromuscular disorders
O_2	Oxygen
pCO_2	Carbon dioxide partial pressure
P_{pl}	Pleural pressure
PSG	Polysomnography
QoL	Quality of life
SMA	Spinal muscle atrophy—congenital myopathy
SNIP	Sniff nasal inspiratory pressure
SpO_2	Pulsatile oxygen saturation
VC	Vital capacity

G. Cinnella · G. Gambetti · M. Rauseo (✉)
Department of Anesthesia and Intensive Care, University of Foggia, Azienda Ospedaliero-Universitaria Ospedali Riuniti, Foggia, Italy
e-mail: gilda.cinnella@unifg.it; michela.rauseo@unifg.it

44.1 Introduction

Neuromuscular disorders are a heterogeneous group of life-limiting diseases causing progressive muscular impairment. In the long term they can even affect respiratory muscles, thereby evolving into respiratory failure [1, 2].

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_44

Table 44.1 Classification of NMD according to the site of injury

Sites	NMD disorders
Spinal cord/ nerve roots	Acute • Guillain–Barre syndrome • Cervical spinal cord injury • Critical illness neuropathy • Multiple sclerosis • Transverse myelitis • Epidural abscess • Acute poliomyelitis • Paralytic rabies Chronic • Spinal cord injury • Motor neuron disease • Amyotrophic lateral sclerosis • Spinal muscular atrophy • Post-polio syndrome • Chronic inflammatory demyelinating polyneuropathy • Charcot–Marie–Tooth disease
Neuromuscular junction	• Myasthenia gravis • Lambert–Eaton myasthenic syndrome • Congenital myasthenic syndrome • Botulism • Venoms (snake, scorpions, ticks) • Neuromuscular junction blockers • Organophosphorus poisoning
Muscle fibers	• Muscular dystrophies • Myotonic dystrophy • Inflammatory myopathies • Congenital and metabolic myopathies

Of note, respiratory muscle weakness varies highly according to the underlying disease due to the involvement of the muscles that can differ in terms of site, timing, reversibility, and modes of acquisition (Table 44.1) [1].

Regardless of the pattern through which respiratory muscle dysfunction develops, when severe, it invariably leads to respiratory insufficiency requiring mechanical ventilation [3].

44.2 Discussion and Analysis of Main Topics

44.2.1 Pathogenesis

There are three groups of respiratory muscles that can be affected:

1. Inspiratory muscles
   - Diaphragm.
   - Parasternal muscles.
   - Scalene muscles.
   - Accessory muscles.
2. Expiratory muscles
   - External intercostal muscles.
   - Abdominal muscles.
3. Muscles of the upper airway
   - Palatine muscles.
   - Pharyngeal muscles.
   - Genioglossal muscles.

The involvement of each group of respiratory muscles has well defined roles in the pathogenesis. Inspiratory muscles impairment, for example, leads to alveolar hypoventilation that can result in hypoxemia and hypercapnia. Expiratory muscles involvement can also contribute to alveolar hypoventilation since it is usually followed by secretions retention as a result of ineffective coughing. The latter prevents the patient from protecting the airways from aspiration of saliva and food particles, which usually takes place as a consequence of upper airway muscle impairment. At this point, it is clear how patients affected by neuromuscular diseases have an increased rate of respiratory infections contributing to a further increase in the work of breathing that can lead to respiratory failure [3, 4].

Taking a look at the respiratory mechanics, two overlapping processes seem to occur. On one side, micro-atelectasis and decreased thorax compliance secondary to deformities caused by chest wall muscles weakness tend to increase the work of breathing resulting in inspiratory muscle weakness. By consequence, patients need to generate greater pleural pressures (P_{pl}) to generate inspiratory flow at the same time having a compromised ability to generate maximal inspiratory pressure (MIP). In these patients, the P_{pl}/MIP ratio is in fact invariably increased. The other mechanisms contributing to the development of chronic, progressive respiratory failure can be attributed to a decreased respiratory muscular response. The presence of an apnea/hypopnea sleep pattern, caused by the combination of respiratory muscle weakness and upper airway

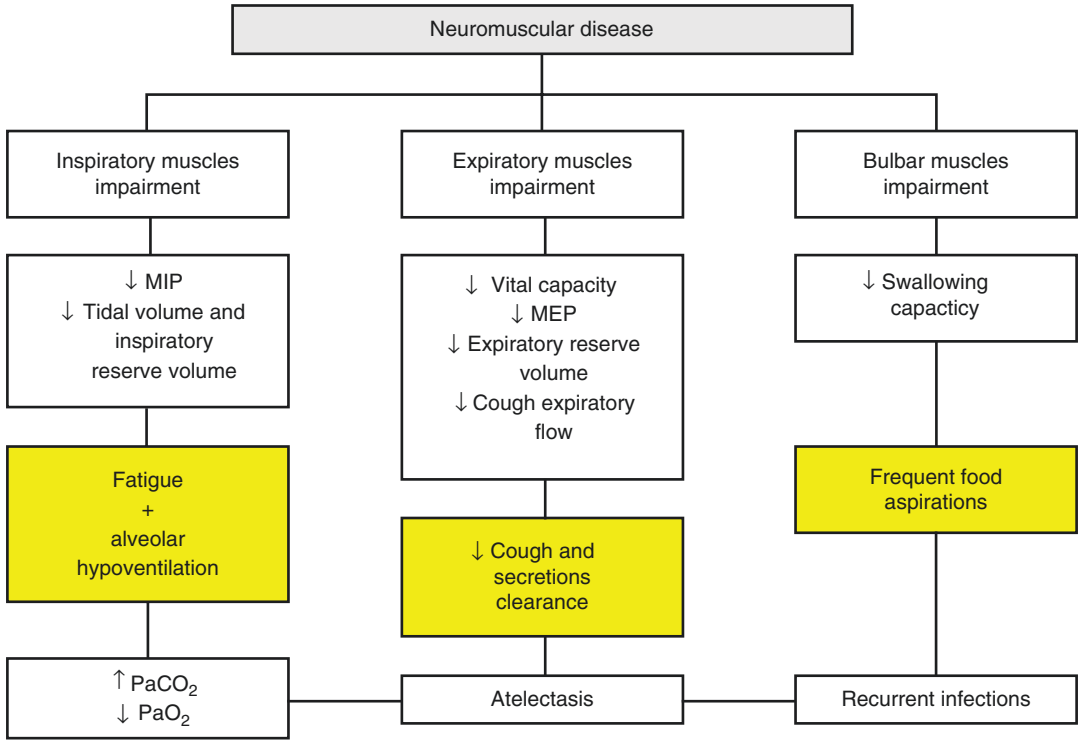

Fig. 44.1 Impairment of different respiratory muscles groups in NMDs and their influence on pathogenesis

obstruction, leads to chronic CO_2 retention, which causes a reduction in respiratory drive. Interestingly, this could only represent an adaptive mechanism aimed to decrease the work of breathing, thereby preventing the development of inspiratory muscle exhaustion [3].

Lastly, patients with progressive NMD can often develop chest and spinal deformities that could increase thoracic impedance and to a further raise of the breathing effort (Fig. 44.1) [1, 3].

44.2.2 Clinical Presentation

Neuromuscular diseases have a different presentation depending on the speed through muscle weakness develops (Table 44.2). In the subacute forms, dyspnea and orthopnea are the prevailing symptoms. However, respiratory arrest can even occur. These respiratory manifestations, which are usually accompanied by symptoms of bulbar weakness and inability to clear secretions, can

Table 44.2 Signs and symptoms suggestive of NMD

Signs	Symptoms
Tachypnea	Dyspnea to minimal effort or speech
Use of accessory respiratory muscles	Orthopnea
Thoraco-abdominal paradox	Frequent nocturnal awakenings
Reducing amplitude of thoracic movements	Disturbed sleep and nightmares
Weak sniff	Daytime sleepiness and fatigue
Poor cough	Morning headaches
Sweating	Apathy, loss of appetite
Tachycardia	Learning difficulties (in children)
Weight loss	Daily concentration deficiency and memory impairment
Dry mouth or hypersalivation	Impaired speech
	Difficulty to expectorate secretions
	Recurrent pneumonia

initially be overlooked. When alveolar hypoventilation develops gradually, it in fact occurs first during sleep and could be suspected on the basis of a broken sleep pattern, nocturnal confusion, morning headache, daytime fatigue, mental clouding, and somnolence [2].

Several clinical signs could be identified just by carefully observing the patient. It may appear overtly breathless, and activation of accessory respiratory muscles even in the form of paradoxical abdominal motion can be noted. When interviewed, the patient may be unable to complete sentences or even take deep breaths when asked to. A significant decrease in vital capacity (VC) or forced vital capacity (FVC) can be suspected when the patient is unable to count from 1 to 20 in a single breath. Somnolence and mental clouding may be also noted as a consequence of the combination of hypoxemia and respiratory acidosis. Inability to clear secretions and limb weakness can be present as a consequence of bulbar and limbs muscles involvement, respectively [2].

44.2.3 Monitoring the Evolution

Classically, patients affected by NMD can be divided in three groups, which dictate the frequency of clinical and instrumental evaluations:

- Ambulant patients who can walk without external assistance.
- Non-ambulant patients unable to maintain the sitting position without help.
- Non-ambulant patients who can stay seated without assistance but need help for walking.

Generally, a respiratory evaluation is recommended every 3–6 months, with a frequency depending on the rate of progression and clinical gravity.

Several instruments are available, such as:

- Pulse oximetry.
- Arterial blood gases.
- Spirometry and capnography.
- Polysomnography (PSG).
- Measurement of MIP and maximum expiratory pressure (MEP).
- Sniff nasal inspiratory pressure (SNIP).
- Cough peak flowmetry.

Spirometry and lung function testing can be useful in detecting a reduction in FVC and monitoring the diseases' course, especially when performed in supine position. While a decreased VC < 1.11 liters has been related to an increased risk of respiratory infections, a VC < 680 mL is a very sensitive indicator of daytime hypercapnia. The decline in VC from sitting to supine position could even be a useful follow-up tool [2, 5]. Moreover, a cough expiratory flow <270 ml/min may warn about ineffective coughing. Pulse oximeters are simple tools that can be useful for detecting hypoxemia during the day and nighttime. The occurrence of a SpO_2 < 94% suggests that clearance of the airways may be needed; however, continuous monitoring has not been suggested yet.

At the same time, if SpO_2 is lower that 94% in a patient who does not have a lung disease, the execution of a blood gas analyses may highlight an eventual concurrent hypercapnia. However, noninvasive methods (i.e., capnography) can be preferred for pediatric patients.

When sleep disorders are suspected, PSG could be indicated and the result actually constitutes the most reliable indicator that NIV should be initiated. However, PSG may not be routinely available, so the use of a cardiorespiratory polygraph could be recommended. It is important though that at least O_2 saturation, heart rate, nasal flow, and chest movements could be registered.

The strength of respiratory muscles can be measured through the evaluation of MIP, MEP, and SNIP. A joint evaluation is strongly suggested since in patients affected by NMD with a prevalent impact on bulbar muscles, a discrepancy between MIP and SNIP could occur. In these cases, the highest pressure should be registered [2]. However, there is no clear evidence regarding the best method to measure MIP. Currently plateau pressures sustained more than 1 second and measured at residual volume are usually recommended [5].

44.2.4 Indications for NIV

Several studies have been made to establish the correct timing to initiate NIV. Current evidence suggests that awaiting the onset of daytime hypercapnia before beginning NIV might be risky. However, the prophylactic use of NIV before the onset of symptoms or nocturnal hypoventilation could offer no additional benefit. A correct time for initiation could be the onset of nocturnal hypoventilation, demonstrated by sustained nocturnal oxygen desaturations [3, 5]. More specifically, in symptomatic patients, NIV must be initiated when at least one of the following is present:

- Signs and symptoms or respiratory disturbances in a patient with NMD.
- Nocturnal desaturation to $SpO_2 \leq 88\%$ for at least 5 consecutive minutes in room air.
- $PaCO_2$ in the morning ≥45 mmHg.
- FVC < 50% predicted.
- MIP or SNIP <60 cmH_2O.

Other indications for NIV may be:

- FVC < 80% of predicted + signs/symptoms of respiratory compromise.
- MIP or SNIP <65 cmH_2O for males and 55 cmH_2O for females + signs/symptoms of respiratory impairment.

For patients with amyotrophic lateral sclerosis (ALS), NIV can be indicated in the presence of nocturnal $SpO_2 \leq 90\%$ for at least 1 cumulative minute or MIP < 60 cmH_2O or both, and FVC < 50% predicted [1, 2].

44.2.5 Contraindications for NIV

Contraindications for NIV in patients with NMD can be very similar to those with other conditions. They include:

- Respiratory arrest or rapid progression of acute respiratory failure.
- Severely impaired mental status (usually GCS < 8).
- Inability to protect the airway, in the form of:
  - Inefficient cough or swallowing with chronic aspiration.
  - Excessive airway secretions.
  - Need for continuous or almost continuous ventilation.
- Hypotension or shock.
- Massive upper gastrointestinal bleeding or vomit.
- Multiorgan failure.
- Physiological/pathological facial features that prevent a proper mask application (i.e., burns/trauma/recent surgery).
- Lack of motivation, by the patient or the family.
- Inability to cooperate or understand the procedure [1, 3].

44.2.6 Choosing the Ventilator

When long-term NIV is indicated, the clinician must choose among several types of ventilators including:

- Pressure-support ventilators, delivering varying tidal volumes depending on the chosen support pressure and the NMD pattern, affecting lung and chest wall compliance.
- Volume-targeted ventilators, which deliver a specified tidal volume for each breath.
- Hybrid mode ventilators: pressure-targeted, volume-granted.

The most used pressure-support ventilator model in NMD patients is surely the bilevel positive airway pressure ventilator (BiPAP). The machine, initially developed to improve patient's tolerance to high CPAP pressures in individuals with OSA, cycles between preset levels of inspiratory and expiratory positive airway pressures (IPAP and EPAP respectively) [2, 4]. It has been shown how BiPAP can effectively improve stabilization of the upper airway, which often is compromised in NMD patients, and reduce atelectasis

[2, 6]. Even if there is insufficient evidence to prefer one type of ventilator, pressure-support ventilators generally provide more comfort and tend to be lighter and cheaper [2].

An example of hybrid mode ventilator is represented by the intelligent volume-assured pressure support (iVAPS). The main feature is represented by the ability to automatically adjust the pressure support to achieve a target ventilation. When compared to BiPAP this mode can lead to higher overnight compliance by improving patient-ventilator synchrony. However no difference was found in spirometry, respiratory muscle strength, sleep quality, arousals, or desaturations [2].

44.2.7 Choosing the Interface

Choosing the right interface is maybe the most important factor to grant adherence to treatment and maximize synchrony between the patient and the ventilator.

When low to moderate pressure support is needed (< 20 cmH_2O), i.e., in cooperative patients with low severity of disease or in children, nasal mask and pillow mask could represent a good choice. They in fact preserve the possibility for the patient to interact with her caregivers, speak, eat, cough, and clear secretions. However it should be noted how nasal mask are more prone to leaks, thereby causing asynchronies, and could have a limited efficacy in patients with nasal obstructions or deformities [2]. Moreover nasal mask could cause nasal dryness and irritation to the bridge of the nose, although the latter complication has been greatly reduced by the introduction of innovative materials [4].

For patients who are less cooperative and have more or less severe NMD, orofacial masks could be best suited. Encompassing both nose and mouth they could be particularly useful in mouth-breathing patients. However, they surely are more uncomfortable, without preserving the ability to talk and to eat, and they may be contraindicated in claustrophobic patients [2].

44.2.8 Adverse Effects and Complications

Adverse effects are usually mild in gravity and are commonly related to the interface, occurring more frequently when nasal and oronasal masks are used. The most common are claustrophobia, skin irritation, pressure ulcers on the nose, nasal congestion, dryness of the nose, and/or the mouth and eye irritation. Despite their frequency, their occurrence could be reduced by the use of simple interventions, like changing the interface frequently or employing humidifiers [2, 3].

Other less common complications are hemodynamic compromise, and pneumothorax and aspiration pneumonias (frequency < 5%) [2].

Finally, healthcare staff should remember to check respirators frequently, as one death due to respirator malfunctioning has occurred [3].

44.2.9 Monitoring NIV Therapy

Monitoring represents a crucial step to maximize NIV compliance and benefits. At the present time, there is no clear evidence suggesting a best strategy to monitor NIV efficacy in NMD [7]. Continuous oximetry, capnography, and blood gases represent the minimum requirements for a sleep study. The frequency, however, depends on the disease course [2].

A specific algorithm has been proposed by the European SomnoNIV Group, including oximetry as the first screening tool in order to select patients needing further nocturnal investigations. For example, successful ventilation has been defined if an improvement of daytime hypercapnia and a mean nocturnal SpO_2 < 90% for at least 90% of the time. However, SpO_2 may not be the most sensible parameter to screen for nocturnal hypoventilation due to a weak relationship with outcomes. A far better parameter could be represented by nocturnal capnometry. The reason could be represented by the fact that NMD pathogenesis reflects mainly the model of restrictive respiratory failure, without underlying lung dis-

ease. Decreases in pO_2 thereby occur on the flat portion of the hemoglobin dissociation curve and are poorly reflected by the changes in SpO_2 [7].

The American Academy of Sleep Medicine even recommends PSG as the best tool to monitor NIV, although costs and limited availability could hamper this practice. Luckily, most of the home NIV ventilators available on the market are now equipped with software able to register data regarding adherence to the therapy, leaks, apnea/hypopnea index (AHI) along with other ventilator parameters. Some even have internal oximeters making the data registered very similar to those obtained by PSG [7].

44.2.10 Quality of Life, Lung Function Measurements, and Other Outcomes

NIV has been effective in improving breathlessness on exertion, quality of sleep, and the occurrence of related symptoms such as daytime sleepiness and early morning headaches among patients with chest wall disorders. An improvement in the activities of daily living was also registered, along with the possibility to continue schooling and returning to work. Psychosocial and mental function can ameliorate as well. Shifting the attention to physiological parameters, sleep architecture, SpO_2, transcutaneous pCO_2, and blood gases often improve just after few days of treatment. Small improvements in vital capacity, functional residual capacity, MIP and MEP, inspiratory muscle endurance, and respiratory drive have also been registered. Even pulmonary hemodynamics has been show to improve after 1 year. Data on survival in patients suffering from chest wall disorders and ventilated with NIV come mainly from uncontrolled studies, showing around 90% 1-year survival and around 80% 5-year survival, depending mainly on the NMD causing the specific chest wall disorder [6].

In patients affected by non-progressive and slowly-progressive NMD (i.e., previous poliomyelitis), NIV has been capable to significantly improve daytime and nocturnal arterial gas values, mortality, and quality of life. Survival rates for patients with previous poliomyelitis almost reach near 100% at 5 years [6].

The use of NIV in progressive NMD, i.e., Duchenne muscular dystrophy (DMD), has for long time indeed been questioned, with some clinicians fearing that the use of a ventilator in a terminal stage of the disease might simply protract death rather than extent good quality life. Recommendations on this topic are mainly derived from case series data since in some instances randomized controlled trials may even be unethical. However, while patient selection remains of critical importance, NIV has been shown to improve quality of life and symptoms in some cohorts. Patients affected by DMD and ventilated with NIV have shown similar health-related quality of life (HRQOL) to age-matched controls and other non-progressive NMD patients, with most of them judging their quality of life as satisfactory. Although poor data is available regarding the impact of NIV on the evolution of cardiomyopathy, lung function, respiratory muscle strength, and functional impairment, 1-year survival and 5-year survival of DMD patients using NIV have been registered to be 85% and 73%, respectively [6].

Amyotrophic lateral sclerosis (ALS) is another progressive NMD which differs from DMD by having a more rapid course, making psychological and physiological adaptations more challenging. Evidence regarding the impact of NIV in this cohort of patients is really limited but shows how substantial improvements in quality of life could be achieved despite the progressive worsening of physical function. When NIV is used, a slower decline in vital capacity can be registered, suggesting that NIV should be indicated when FVC falls below 50% of the predicted. It should be noted, however, how NIV failure rates in patients affected by ALS are significantly higher than in other NMD, especially for those with moderate to severe bulbar symptoms [6, 8]. This has also been demonstrated by a recent observational study investigating the 5-year outcomes of different NMD patients ventilated with NIV [8]. For example, 5-year NIV maintenance rates were 91% for spinal muscle atrophy (SMA)-congenital

myopathy, 89% for DMD, and 23% for ALS. At the same time average NIV maintenance durations were 21.5 ± 19.3 months, 55.2 ± 11.5, and 57.5 ± 8.3 months, respectively, with a high proportion of patients tolerating NIV. Due to the natural course of the disease, NIV duration significantly increased in patients affected by ALS while in DMD and SMA-congenital myopathy groups only a trend toward increase was registered. 5-year survival rate was similar in DMD, SMA-congenital myopathy, and other NMDs (near 90%) while it was only 38% in ALS patients. While the authors also compared FVC measurements at NIV initiation and after 5 years, which significantly decreased in all patients except for those affected with SMA-congenital myopathy, no data regarding quality of life was registered [8].

An interesting study by the Italian group of Crescimanno et al. has tried to understand the relation between several lung function measurements and QoL in adult patients affected by DMD and receiving long-term NIV [9]. For the evaluation of quality of life the authors used the Individualized Neuromuscular Quality of Life questionnaire (INQoL), a tool developed in a heterogeneous group of patients affected by congenital and inflammatory myopathies and muscular dystrophies, including those progressed to respiratory failure. Physical health and areas of life were the most affected domains, the loss of independence the most highlighted concern, whereas the psychosocial domain was relatively preserved [9]. Among the lung function parameter studies, MIP emerged as the only independent predictor of global INQoL. SNIP was also correlated to INQoL sections, but less often than MIP and not to the global INQoL score. It may suggest, however, that ameliorating respiratory function in these patients would also improve their quality of life. The second significant independent predictor for global INQoL was represented by sleep quality, especially in relatively old DMD patients. Thereby efforts aiming to improve sleep in these patients could ensure them a better QoL. The psychosocial aspect was indeed the least affected domain of INQoL, maybe due to good support and care given to these patients. Finally, age was correlated only to the physical domain of the INQoL but not with the other, suggesting a relation mediated by the common—and physiological—worsening of respiratory function [9].

Few data are indeed available in the pediatric population. For this reason, a very recent study by Johannsen et al. has investigated the health-related quality of life and mental health of ventilated and non-ventilated children with NMDs and their families [10]. In their work the authors showed how children with NMDs and their parents reported reduced child's overall QoL, especially regarding physical and psychological well-being and social integration, even lower to other children with different chronic conditions [10]. Interestingly, however, the results were not related to the need of mechanical ventilation suggesting how ventilator use per se had no negative influence on patients HRQOL and mental health. These data even support an improvement in QoL and physical performance after initiation of NIV, especially in the later stages of the disease [10]. However, the impact and the course of different NMDs and other underlying conditions should be always kept in mind. In ventilated children a reduction in the contact with peers was reported only by the parents but not by the children themselves. HRQOL and mental health related outcomes of parents were only slightly decreased with no relationship to the use of mechanical ventilation in their children. However, the results may have been influenced by several other factors, including social comparison, external support, family dynamics, and relations [10].

44.3 Conclusion Discussion

In patients affected with NMDs, NIV represents an effective tool to improve gas exchange, respiratory pattern, and quality of life. In this cohort of patients, the change in several lung function measures used to monitor the evolution of the disease seems even to reflect the impact of NIV on several domains of health-related quality of life. This surely reflects how QoL in NMD patients is

strongly affected by the degree of their respiratory impairment. Among these parameters, vital capacity, maximal inspiratory pressure, and sniff nasal inspiratory pressure seem to have the most reliable relationship with HRQOL.

Key Major Recommendations

- The progressive muscular impairment caused by NMDs could even evolve into respiratory failure, whose manifestations should be actively searched by the clinician.
- Several lung function indices are used to monitor the progression of the disease. Among these, polysomnography is the best tool to monitor for nocturnal hypoventilation.
- When signs or symptoms of hypoventilation, prolonged nocturnal desaturations, and/or significant alteration in lung function parameters are registered, NIV therapy should be started promptly.
- As in other conditions characterized by respiratory failure, the correct choice of a NIV interface plays a key role in maximizing the efficacy of the therapy.
- The same lung function indices used to monitor disease progression have been found correlated with NIV efficacy and HRQOL. Among all the therapeutic resources available, the effective management of respiratory compromise could have the strongest impact on the quality of life of NMD patients and their families.

References

1. Regunath H, Diseases I, Whitacre T, Services RT, Whitt SP. Sleep issues in neuromuscular disorders. Sleep Issues Neuromuscul Disord. 2018.
2. Davidescu L, Manolescu D, Ulmeanu R, Oancea C. Noninvasive ventilation in neuromuscular disease. In: Vats M, editor. Noninvasive ventilation in medicine—recent updates. IntechOpen; 2018. p. 21–40.
3. Lisboa C, Díaz O, Fadic R. Noninvasive mechanical ventilation in patients with neuromuscular diseases and in patients with chest restriction. Arch Bronconeumol. 2003;39(7):314–20.
4. Bonekat W. Noninvasive ventilation in neuromuscular disease. Crit Care Clin. 1998;14(4):775–97.
5. Ambrosino N, Carpenè N, Gherardi M. Chronic respiratory care for neuromuscular diseases in adults. Eur Respir J. 2008;34(2):444–51.
6. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J. 2002;20(2):480–7.
7. Crimi C, Pierucci P, Carlucci A, Cortegiani A, Gregoretti C. Long-term ventilation in neuromuscular patients: review of concerns, beliefs, and ethical dilemmas. Respiration. 2019;97(3):185–96.
8. Suh MR, Choi WA, Kim DH, Lee JW, Kim EY, Kang SW. Five-year follow-up and outcomes of noninvasive ventilation in subjects with neuromuscular diseases. Respir Care. 2018;63(3):274–81.
9. Crescimanno G, Greco F, D'Alia R, Messina L, Marrone O. Quality of life in long term ventilated adult patients with Duchenne muscular dystrophy. Neuromuscul Disord. 2019;29(8):569–75.
10. Johannsen J, Fuhrmann L, Grolle B, Morgenstern L, Wiegand-Grefe S, Denecke J. The impact of long-term ventilator-use on health-related quality of life and the mental health of children with neuromuscular diseases and their families: need for a revised perspective? Health Qual Life Outcomes. 2020;18(1):1–11.

45 Relationship of Pulmonary Function Testing to Emotional and Psychosocial Factors

Marilena De Guglielmo, Giuseppina Fabbo, and Andrea Fabbo

Abstract

Recently evidence-based recommendations for the most common lung function assessments take into account patient-related psychosocial, psychological and neuropsychiatric factors that may influence both the performance and interpretation of lung function tests. We discuss the assessment of these factors that must be evaluated by the clinician not only to determine the patient's respiratory profile but also to identify any problems (such as alterations in mental status, delirium, cognitive deficits and psychological problems) that could affect both therapeutic adherence and efficacy of NIV.

Keywords

Noninvasive ventilation · Health-related quality of life · Multidimensional evaluation

Psychosocial factors in respiratory diseases
Cognitive impairment

Abbreviations

ACE-R	Addenbrooke's Cognitive Examination Revised
ARF	Acute respiratory failure
ARTP	Association for Respiratory Technology and Physiology
BDI	Beck Depression Inventory,
BMI	Body mass index
CAM	Confusion Assessment Method
CDT	Clock Drawing Test
CES-D	Center for Epidemiologic Studies-Depression Scale
CGA	Comprehensive Geriatric Assessment
COPD	Chronic obstructive pulmonary disease
CRD	Chronic respiratory diseases
EGA	Emogasanalysis
EQ-5D	Euro Quality of Life-5 Dimensions
EXIT	Executive Interview
FAB	Frontal Assessment Battery
FCV	Forced vital capacity
FEV	Forced expiratory volume
FSS	Fatigue Severity Scale
GDS	Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale

M. De Guglielmo
Pneumological Service, Primary Care Department, Health Authority and Services, Modena, Italy

G. Fabbo
San Giovanni di Dio and Ruggi d'Aragona Hospital, University of Salerno "Scuola Medica Salernitana", Salerno, Italy

A. Fabbo (✉)
Geriatric Service, Cognitive Disorders and Dementia Unit, Health Authority and Services, Modena, Italy
e-mail: a.fabbo@ausl.mo.it

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_45

HCO_3	Hydrogen carbonate concentration
HRQL	Health-Related Quality of Life
IADL	Instrumental Activities of Daily Living
MCI	Mild cognitive impairment
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
mMRC	Modified Medical Research Council Dyspnea Scale
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRF-26	Maugeri Respiratory Failure Questionnaire
NIV	Noninvasive ventilation
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood,
PaO_2	Partial pressure of oxygen in arterial blood
PEF	Peak expiratory flow
PFTs	Pulmonary function tests
pH	Potential of hydrogen
SGRQ	St George's Respiratory Questionnaire
SRI	Severe respiratory insufficiency

45.1 Introduction

Noninvasive ventilation (NIV) is currently one of the most commonly used support methods in hypoxaemic and hypercapnic acute respiratory failure (ARF). With advancing technology, increasing knowledge and clinical evidence, not only the indications for NIV are on the rise but more patients are treated with this methodology. However, it is important to remember that patients with ARF are always very frail with possible high mortality risk. Therefore, it is crucial to know all the implications that determine the efficacy of NIV including the relationship between pulmonary function test and clinical, psychological and environmental factors [1]. Pulmonary function tests (PFTs) allow physicians to evaluate the respiratory function of their patients. Current tests (*spirometry* that measures forced vital capacity (FVC) and forced expiratory volume (FEV), *diffusion capacity* that studies the diffusion of gases across the alveolar-capillary membranes, the *respiratory muscle pressures* such as the maximal inspiratory pressure (MIP), the maximal expiratory pressure (MEP) and the *peak expiratory flow* (PEF with vital capacities measured in the upright (-U) and supine (-S) position) are reproducible and accurate but their results are influenced by the level of cooperation and effort of patients. PFTs, in addition to helping to reach a diagnosis together with the history and clinical evaluation of the patients, also allow physicians to quantify the severity of the pulmonary disease, follow it up over time and assess its response to pharmacological and non-pharmacological treatments. PFTs also provide prognostic information, with lung function measures predicting mortality and the development of clinical complications. The results of the PFTs might not be accurate if there is lack of cooperation or poor ability to understand instructions from the patient. Also, if patients have an acute illness or symptom (for example, altered mental status, delirium, anxiety or depression or stressful conditions such as panic attack or anger) they are likely to have suboptimal results. Recently the Association for Respiratory Technology & Physiology (ARTP) published the most up-to-date and evidence-based recommendations for the most common lung function assessments; these recommendations take into account patient-related environmental and psychosocial factors that may influence both the performance and interpretation of lung function tests [2]. In this chapter we discuss the assessment of emotional, neuropsychiatric and psychological factors that must be evaluated by the clinician not only to determine the patient's respiratory profile but also to identify any problems (such as alterations in mental status, delirium, cognitive deficits and psychological and psychosocial factors) that could affect both therapeutic adherence and efficacy of NIV. This situation is even more relevant for older patients who represent a potentially broad category in need of this therapeutic intervention. Another factor to consider is the involvement of the family caregiver; a study conducted on patients with motor neuron disease who needed NIV showed that psychological support and proactive involvement of family care-

givers (particularly caregiver resilience) in the management of the disease improve acceptance and optimization of NIV treatment [3].

45.2 Discussion and Analysis of the Main Topics

45.2.1 The Assessment of Emotional, Neuropsychiatric and Psychosocial Factors

In order to verify the conditions that could limit acceptance and adherence to NIV, the assessment of the patient will have to foresee, according to a recent study, the socio-demographic conditions, the medical problems and clinical evaluation associated with respiratory function tests, the psychological rating with validated tests including also quality of life and a cognitive and behavioural assessment [4]. At the first evaluation of the patient, it is important to collect information regarding the socio-demographic profile such as age, gender, weight, level of education, current and previous employment condition, cohabitation, lifestyle information, levels of physical activity, duration of disease, drug therapies (paying particular attention to the investigation on the use of psychotropic drugs), comorbidities and the number of hospital admissions during the last year. Medical evaluation should include respiratory function tests such as simple spirometry, emogasanalysis (EGA) and fatigue. Spirometry allows the evaluation of the following parameters: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and Tiffeneau index (FEV1/FVC ratio). EGA provides information on the potential of hydrogen (pH), partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and hydrogen carbonate concentration (HCO_3). Fatigue is a primary disabling symptom in chronic respiratory diseases (CRD) with major clinical implications. However, fatigue is not yet sufficiently explored and is still poorly understood in this area, making this symptom often underdiagnosed and undertreated. Most studies in CRD evaluated perceived fatigue as a trait characteristic using multidimensional scales, providing precious information about its prevalence and clinical impact. These multidimensional scales also provide evidence that fatigue in CRD is distinguishable from other related symptoms also prevalent in these people, such as sleepiness, dyspnoea, anxiety and depression which must however be considered in the global assessment of these patients. Many fatigue rating scales have been considered in the literature but to date the ideal tool has not been found because fatigue is an unstable, dynamic phenomenon which can result from various real-life situations with varying degrees of severity. In fact, the evaluation of this symptom is affected more than others by psychosocial and emotional factors such as depression, anxiety and stress as well as factors that affect the quality of life of patients. Fatigue can have both a pathophysiological basis that includes brain mechanisms or metabolic exhaustion [5] and a psychological basis that identifies it as a consequence of stress [6]. A widely used test is the Fatigue Severity Scale (FSS) which has shown good psychometric properties and the ability to detect change over time [7, 8]; this tool consists of nine items which measures the severity of symptom ‘fatigue’ and its effects on a person’s ability to carry out daily activities and lifestyle habits in patients with a variety of disorders. The items are scored on a seven point scale with 1 = strongly disagree and 7 = strongly agree; the higher score (the score ranges from a minimum of 9 to maximum of 63) indicates a more severe severity level of the fatigue. It has also been shown that the FSS-7, used in rehabilitation settings, showed better psychometric properties and had better potential to detect changes in fatigue over time than the FSS-9 version [9]. Particularly important may be the measurement of anxiety and depression (frequently associated with respiratory diseases) that can affect respiratory function. At present there are confirmations which indicate the importance of mood depression to negatively interfere, sometimes in an important way, with the ability of the patient to adhere to a program of respiratory rehabilitation or more complex treatments such as NIV; in fact, one in three patients does not

complete the respiratory treatments due to a concomitant depressive disorder. Furthermore, these studies report, in COPD patients, a higher mortality in the class of those who do not follow a respiratory rehabilitation program or other treatments compared to those who instead complete it [10]. It has been identified an inverse association of depressive symptoms and pulmonary function in healthy adults especially in men and individuals with a heavy smoking history and chronic lung disease is often exacerbated by comorbid psychiatric issues; in fact the treatment of depression may improve pulmonary disease symptoms [11]. For this reason it is important a preliminary assessment of mood is done in respiratory patients (especially patients with COPD respiratory failure) potentially eligible for long-term treatments. The Hospital Anxiety and Depression Scale (HADS) is one of the most used and known tools for measuring anxiety; although the HADS questionnaire was originally developed to measure anxiety and depression in non-psychiatric patients treated in hospitals, it has also been reported to be valid in other health care settings such as home care or long-term care facility [12, 13]. HADS could be a useful screening tool for use in non-psychiatric patients to identify patients with emotional distress. The HADS consists of 14 questions of which 7 measure symptoms of anxiety and 7 measure symptoms of depression during the previous week and are given using a four-point scale (0, 1, 2, 3) and total score for each subscale ranges from 0 to 21; in fact the tool is organized into two 7-item subscales: HADS-A and HADS-B which generate separate sub-scores for anxiety and depression, respectively. A score between 0 and 7 indicates 'normal state', a score between 8 and 10 a 'borderline state' whereas a score between 11 and 21 an 'anxiety state'. Some studies have shown that anxiety symptoms and respiratory function are independently associated with reporting dyspnoea [14]. Other quick assessment tools could be the CES-D and the short version of the Geriatric Depression Scale. The CES-D scale is a brief self-report scale designed to measure self-reported symptoms associated with depression experienced in the past week. The items of the scale are symptoms associated with depression (such as anxiety, sleep disturbances, fatigue, loneliness, easy crying) which have been used in previously validated longer scales, but some investigations, despite their popularity, highlighted the need for revision on some items indispensable for the diagnosis of depression [15]. Due to the presence of increasingly older patients with respiratory problems who could be candidates for NIV, it could be useful to use tools more suitable for this population such as the Geriatric Depression Scale. The GDS original form is a brief, 30-item questionnaire in which patients are asked to respond by answering 'yes' or 'no' in reference to how they felt over the past week. The most used and fastest version is the 'Short Form GDS' consisting of 15 questions which was developed some years ago. Questions from the Long Form GDS which had the highest correlation with depressive symptoms in validation studies were selected for the short version. Scores of 0–4 are considered normal, depending on age, education and complaints; 5–8 indicate mild depression; 9–11 indicate moderate depression and 12–15 indicate severe depression. The GDS may be used with healthy, medically ill and mild to moderately cognitively impaired older adults. This assessment tool can be used in a wide range of patients, and it has been extensively used in community, acute and long-term care settings [16]. The most widely used assessment tools for depression is the Beck Depression Inventory (BDI) which evaluates a patient's emotional, cognitive, motivational and physiological status. The BDI has a high sensitivity and specificity for diagnosing depressive symptoms and it consists of 21 self-reporting items, and the score ranges from 0 to 63 with higher scores reflecting greater levels of depression [17]. A Korean study showed that a higher BDI score was associated with a lower FEV1 after adjusting for age, sex, body mass index (BMI) and smoking status, and there is a correlation between the severity of depression and FEV1, especially in adults older than 50 years [18]. Emotional stress-related factors such as anger should also not be underestimated; in fact a relationship between decline in lung function in older men and the emotional characteristic of anger has been discussed, and

there is considerable evidence for a relationship between negative emotion (anger, anxiety, sadness) and deterioration in pulmonary function probably through a chronic dysregulation. However, it has not yet been clarified the exact pathway by which this happens [19]. In addition to the assessment of the medical condition (body mass index (BMI), arterial blood gas, pulmonary function, dyspnoea) and psychological status (anxiety, depression and stressful situations) measuring quality of life can be significant through the use of patient-reported measurements of HRQL (Health-Related Quality of Life). Among the most well-known tools we mention are the SGRQ (St. George's Respiratory Questionnaire) [20], the SRI (Severe Respiratory Insufficiency) questionnaire [21] and the MRF-26 (Maugeri Respiratory Failure) questionnaire [22]. The SGRQ was originally developed for patients with chronic airflow limitation such as COPD and was subsequently validated for other breathing problems. This disease-specific instrument has three components: symptoms, activities and impact which are added together in a total score; in fact it was designed to measure impact on overall health, daily life and perceived well-being in patients with obstructive airways disease. The Severe Respiratory Insufficiency (SRI) questionnaire consists of seven subscales: respiratory complaints (eight items), physical functioning (six items), attendant symptoms and sleep (seven items), social relationships (six items), anxiety (five items), psychological well-being (nine items) and social functioning (eight items); one summary scale (SS) is obtained from the sum of the mentioned above subscales. The Maugeri Respiratory Failure (MRF)-26 is a modified version of the original instrument with 28 items (MRF-28) designed for patients with chronic respiratory failure. It has two domains: daily activities and perceived disability, from which the total score is calculated. In each questionnaire, the score ranges from 0 to 100: higher scores indicate a better health-related quality of life in the SRI while in the SGRQ and MRF-26 a higher score indicate more limitations. Another well-known tool used in various diseases is the EuroQoL (EQ-5D), an instrument which evaluates the generic quality of life developed in Europe. This tool allows you to evaluate the quality of life through two sections: in the first section are included five health-related items (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and it is used to assess the severity of health-related problems; the second section, on the other hand, consists of a visual-analogue scale (similar to tools used for pain assessment) that indicates the person's current perception of their state of health (from '0' worst possible health state to '100' best possible health state) [23]. An important parameter is the assessment of dyspnoea during the activities of daily living which can be evaluated with the modified Medical Research Council (mMRC) dyspnoea scale. This scale is very simple and it is based on a 5-point graduation (from "0" to "4") that evaluates various levels of physical activity that precipitate dyspnoea Higher scores indicate worse dyspnoea [24]. A very interesting Japanese study showed that the mMRC (Medical Research Council dyspnoea scale) and HADS (Hospital and Anxiety Depression Scale) were significantly related to all domains of the SRI, MRF-26 and SGRQ. In fact, the SRI and MRF-26 are directly related to physical and psychological impairments in health similarly to the well-known SGRQ, although the MRF-26 had no specific psychological domains. Conversely the links between Health-Related Quality of Life (HRQL) parameters and physiological measurements were not strong, indicating that HRQL indicators are independent of the physiological parameters and cannot be estimated from pulmonary function or blood gases alone [25]. In a longitudinal analysis in patients receiving NIV, although both the SRI and MRF-26 strongly predicted mortality, the SRI only (but not the MRF-26) was able to predict mortality independently of physiological and respiratory function parameters such as BMI (body mass index), FVC (forced vital capacity) and $PaCO_2$ (partial pressure of carbon dioxide) [26]. In summary, these studies have shown that both SRI and MRF-26 were reliable questionnaires in patients with chronic hypercapnic respiratory failure receiving NIV. Dyspnoea and psychological status likewise were their main

determinants while their relations with physiological measurements were weaker. The SRI covers more psychological health problems than the MRF-26. The assessment of the patient selected for NIV must also include cognitive evaluation which can affect both cognitive functions in general or especially executive functions. In fact, executive functions could interest the patient's decision-making abilities in adhering to a certain type of treatment. Cognition involves different cognitive processes which can be divided into some neuropsychological domains including learning and memory, visuospatial and motor function, attention and concentration capacity, language, social cognition/emotions and executive functions. Each domain contains specific functions which provide people with basic information and complex skills that determine personal intellectual capacities and global knowledge. The relationship between lung impairment and cognitive function decline has already been confirmed in numerous studies, which have demonstrated the negative impact of inadequate respiratory function on cognitive domains; these negative consequences on cognitive function are a result of complex interactions between lung pathophysiological factors (as it happens in COPD) and genetic and environmental factors [27]. If the oxygen supply is insufficient to satisfy the metabolic demands of the brain due to impaired or inadequate lung mechanics respiratory function (such as in COPD patients), this can trigger the loss of vulnerable brain neurons; in fact, high levels of oxygen desaturation increase the risk of cognitive dysfunction as reported in some studies [28] as well as elevated carbon dioxide tension (PCO_2) levels are associated with lower cognitive performance [29]. Other studies observed that cognitive impairment is significantly worse in both hypoxaemic and non-hypoxaemic COPD patients when compared to healthy individuals [30]. A wide range of tools have been developed for screening cognitive function and the duration of screening ranges from a few minutes up to several hours in the case of a formal neuropsychological assessment. Most of the tests designed for use in prompt cognitive assessment during the daily clinical routine take from 4 to 12 min to be completed. The most widely used tests which explore multiple cognitive domains are the Mini Mental State Examination (MMSE) [31], the Addenbrooke's Cognitive Examination (ACE-R) [32], the Montreal Cognitive Assessment (MoCA) [33] and the Clock Drawing Test (CDT) [34]. The ACE-R (a brief cognitive test that assesses five aspects of cognition such as attention/orientation, memory, verbal fluency, language and visuospatial abilities) is one of the best tests to detect a condition of dementia (or major neurocognitive disorders according to DSM-5) while MoCA has been particularly studied to identify the condition of mild cognitive impairment (MCI or minor neurocognitive disorders according to DSM-5) characterized by the presence of cognitive deficits that do not impact on the activities of daily life [35]. The executive functions are the cognitive ability to determine the performance of skills as well as instrumental activities (IADL) necessary for an independent life (such as e.g., exercise a profession, manage a family, money, use of medications, drive, etc.). Neurocognitive disorders compromise executive functions and must therefore be investigated and monitored. The executive functions and, therefore, the 'competence' can fluctuate during the course of the neurocognitive disorders or during the development of delirium and can been compromised due to various causes: drugs, acute diseases, pain, insomnia or depression. Many tools for the assessment of competency instruments have been developed in research contexts. The cognitive assessment in adult patients without severe mental illnesses showed that the MMSE, developed as a screening tool, known and used all over the world, to detect cognitive failure does not evaluate executive functions. In fact, the executive cognitive dysfunction is typically the first area of cognitive impairment and these problems can precede the other symptoms such as impaired memory or language. People with executive cognitive dysfunction can have a normal MMSE score but still have severe functional limitations. The screening tests evaluating executive functions include the Montreal Cognitive Assessment (MOCA), quick to administer (15–20 min) and

correlates with more comprehensive testing, the Frontal Assessment Battery (FAB) [36] and the Executive Interview (EXIT) [37], both quick to administer (<15 min and 15–20 min, respectively). A formal neuropsychological testing is the gold standard to assess cognitive functions but it is not simple to use in hospital wards because some barriers like time consuming (hours), high cost (requires specialized health professionals), difficult to access and may not well tolerated by patients with comorbid medical or psychiatric conditions. Finally, the assessment of the patient candidate for NIV must also include the assessment for possible delirium, a very frequent condition especially in the elderly hospitalized person. Delirium is a severe neuropsychiatric syndrome characterized by the acute onset of deficits in attention and others cognitive or neurobehavioural symptoms. Despite its high prevalence, it often remains unrecognized; a recent study estimated the rate of undetected delirium to be as high as 60%. Moreover, patients with delirium can be found in all medical or surgical specialties of the hospital [38]. The American Psychiatric Association's fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) revised the diagnostic criteria for delirium, which remains a clinical diagnosis [39]. This includes an acute onset and fluctuating course of symptoms, inattention, impaired level of consciousness and disturbance of cognition, indicating disorganization of thoughts (e.g., disorientation, memory impairment, or alteration in language). The Confusion Assessment Method (CAM) [40] continues to be the most widely used delirium instrument worldwide. The CAM provides an algorithm based on the four core features of delirium: acute onset, fluctuating course of symptoms, inattention and either disorganized thinking or altered level of consciousness. Other characteristics which are supportive of the delirium diagnosis include alterations in the sleep-wake cycle, perceptual disturbances (e.g., hallucinations or misperceptions), delusions, inappropriate or unsafe behaviour and emotional lability). The CAM algorithm has been validated in research and has high sensitivity (94–100%) and specificity (90–95%) with good interrater reliability. The CAM has also been adapted for use in the ICU, emergency departments, nursing homes and in palliative care. A brief assessment for the CAM is the 3-minute diagnostic assessment (3D)-CAM, which provides an assessment via a 20-item checklist with sensitivity of 95% and specificity of 94% in hospitalized patients. Since more factors are involved in the aetiology of delirium, there are probably several neurobiological processes that contribute to the delirium pathophysiology, including neuroinflammation, cerebral vascular dysfunction, impaired brain metabolism, imbalances in neurotransmission and impaired neuronal network connectivity. In patients with respiratory failure and mechanical ventilation, a number of interactions between brain function and respiratory function need to be considered. A cooperative sedation strategy and a multi-professional approach (i.e., the patient is awake and free of pain and delirium) is feasible in many patients requiring invasive mechanical ventilation [41].

45.3 Conclusive Remarks

There is currently much discussion on the role of psychological status and psychosocial factors on lung function tests and how crucial their influences are in determining both adherence and the success of a therapeutic intervention but studies in this area are still scarce. For example, a recent study (that examined factors associated with poor quality of life focusing on psychological measures that can easily be controlled with intervention and treatment) indicates that psychological factors such as symptoms of depression and anxiety (performed with Hospital Anxiety and Depression Scale- HADS) in COPD are associated with lower physical functional performance and poorer lung function in the 6-minute walking test [42]. Some studies suggest that it is necessary to pay attention to psychological factors in both therapy and rehabilitation of respiratory diseases; psychological changes may be a consequence of physical symptoms, but they may also influence the course of illness, as happens in the

majority of chronic diseases [43]. Many studies have confirmed that noninvasive ventilation (NIV) has been found to have a therapeutic goal on some variables such as patient's satisfaction (improvement of symptoms and quality of life), efficacy of ventilatory support (improvement of daytime $PaCO_2$, nocturnal hypoventilation, appropriate nocturnal SpO_2), reduction of respiratory events (no apnoea during NIV, low level of unintentional leaks, optimum patient-ventilator synchrony) and improvement of prognosis (reduction of respiratory morbidity and disease-related burden and improved survival) [44, 45]. Despite these potential positive effects, in addition to the important role of frailty and comorbidity on NIV treatment especially for older people [46], a critical role is offered by neuropsychiatric, psychosocial and emotional factors. Psychosocial factors and mental health wellbeing can influence the pathogenesis and pathophysiology of respiratory diseases either directly through autonomic, endocrine, immunological and central nervous system mechanisms, or indirectly through lifestyle factors, mental health problems, cognitive impairment [47] and NIV management including adherence and reduction of adverse events. The capacity for acceptance of noninvasive ventilation (NIV) is an example of the interaction of psychological and physical factors. Despite the fact that NIV can produce an improvement in clinical condition, patients often reject it or fail to use it appropriately causing worsening of symptoms and increased health care costs. Acceptance and adherence to NIV treatment is crucial because it can reduce the number of prescribed drugs, the hospital admissions and physician visits [48]. There are few studies that have identified the individual psychological factors that increase the risk of rejection or improper use of NIV. An Italian study recently focused on the role of global assessment (including cognitive and behavioural aspects) and psychological support in determining acceptance and adherence to NIV in patients with COPD [49]. Certainly, future research will have to be addressed in this area such as the role of multidimensional assessment tools in the selection of patient candidates for NIV both because of the progressive rise of older patients (who require the typical methodology of the geriatric approach) and of the increasing relevance of neuropsychiatric determinants and psychosocial factors (including health-related quality of life) connected to lung function and related diseases.

Key Major Recommendations

- Psychosocial and emotional (health-related quality of life, environmental factors, low social support, personality, negative feeling such as anger, loneliness and stressful life events, characteristics of the caregiver) and neuropsychiatric symptoms (anxiety, depression, neurological disorders and cognitive impairment) are not rarely associated with chronic lung disease which can lead to respiratory failure. Physical and mental health are strongly interrelated in respiratory diseases. An important role is played by anxiety and depression though the cause-and-effect relationships between these conditions, dyspnoea and respiratory function parameters are unclear. It is likely that these factors may play a mediating role between objective symptoms and respiratory function tests and health-related quality of life. The identification and control of psychosocial, emotional and neuropsychiatric conditions could be an optimal strategy in the management of respiratory diseases including assessing adherence to specific treatments such as NIV. For this reason, a global evaluation of the respiratory patient is recommended. This assessment can be useful to associate the evaluation of the respiratory function parameters with cognitive, behavioural, functional and health-related quality of life through questionnaires and validated scales. The importance of these tools is increasing not only in research but especially in clinical practice.
- The presence of neurobehavioural impairment and delirium are often negative predictors of NIV adaptation. Delirium is a frequent condition associated with patients (especially elderly people) treated with NIV or managed in intensive care unit but it often remains unrecognized. There is a need to learn to rec-

ognize delirium through the use of adequate tools such as CAM both for better patient care and, particularly, for its prevention; in fact, delirium prevention still represents the best management approach in all care settings.

- The cognitive assessment of these patients is proving increasingly necessary; in fact, cognitive impairment is an important limitation in respiratory patients and cognitive deficits (that could limit the effectiveness of therapy) should be considered prior to health care planning. Healthcare professionals in respiratory settings are advised to know how to administer a brief cognitive assessment test to detect cognitive impairment. In particular, executive functions are to be evaluated because they are directly related to the person's ability to manage the activities of daily life linked to problem-solving, thinking and sequencing tasks. Cognitive assessment permits to also define 'decisional capacity' understood as the ability to make a choice, control his/her emotions, the daily life activities and the expression of preferences and wishes.
- Many studies highlight the need for a patient-tailored multidisciplinary approach that includes respiratory function tests, cognitive-behavioural and neuropsychological assessment to optimize patient training and compliance with NIV. The framework of comprehensive geriatric assessment (CGA), which has been shown (compared with usual care) to improve health outcomes of older persons, could be the reference model for the evaluation of complex patients and, in particular, those with respiratory failure who may need NIV but future research is needed to investigate these aspects.

References

1. Ergan B, Nasiłowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev. 2018;27:170101. https://doi.org/10.1183/16000617.0101-2017.
2. Sylvester KP, Clayton N, Cliff I, et al. ARTP statement on pulmonary function testing 2020. BMJ Open Resp Res. 2020;7:e000575. https://doi.org/10.1136/bmjresp-2020-000575.
3. Cousins R, Ando H, Thornton E, Chakrabarti B, Angus R, Young C. Determinants of accepting non-invasive ventilation treatment in motor neurone disease: a quantitative analysis at point of need. Health Psychol Behav Med. 2013;1(1):47–58.
4. Volpato E, Banfi P, Pagnini F. A psychological intervention to promote acceptance and adherence to non-invasive ventilation in people with chronic obstructive pulmonary disease: study protocol of a randomised controlled trial. Trials. 2017;18:59. https://doi.org/10.1186/s13063-017-1802-1.
5. DeLuca J, Genova HM, Capili EJ, Wylie GR. Functional neuroimaging of fatigue. Phys Med Rehabil Clin N Am. 2009;20(2):325–37.
6. Pi IG, Sein-Echaluce MLG, Aubach LR, Puig-Gros JT, Sola JF. Stressful events in the onset of chronic fatigue syndrome. Revista Espanola De Salud Publica. 2016;90:E1–7.
7. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manag. 2009;37(1):107–28.
8. Schwartz JE, Jandorf L, Krupp LB. The measurement of fatigue: a new instrument. J Psychosom Res. 1993;37:753–62.
9. Lerdal A, Kottorp A. Psychometric properties of the Fatigue Severity Scale-Rasch analyses of individual responses in a Norwegian stroke cohort. Int J Nurs Stud. 2011;48(10):1258–65. https://doi.org/10.1016/j.ijnurstu.2011.02.019. Epub 2011 Mar 16
10. Gudmundsson G, Gislason T, Janson C, Lindberg E, Suppli Ulrik C, Brøndum E, et al. Depression, anxiety and health status after hospitalisation for COPD: a multicentre study in the Nordic countries. Respir Med. 2006;100:87–93.
11. Ochs-Balcom HM, Lainhart W, Mnatsakanova A, Charles LE, Violanti JM, Andrew ME, Freudenheim JL, Muti P, Trevisan M, Burchfiel CM, Schünemann HJ. The association of depressive symptoms and pulmonary function in healthy adults. Psychosom Med. 2013;75(8):737–43. https://doi.org/10.1097/PSY.0b013e3182a15672. Epub 2013 Aug 19. PMID: 23960159; PMCID: PMC3797871
12. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
13. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale: an updated literature review. J Psychosom Res. 2002;52:69e77.
14. Leivseth L, Nilsen T, Mai X-M, Johnsen R, Langhammer A. Lung function and anxiety in association with dyspnoea: The HUNT study. Respir Med. 2012;106:1148–57. https://doi.org/10.1016/j.rmed.2012.03.017.
15. Carleton RN, et al. The center for epidemiologic studies depression scale: a review with a theoretical and empirical examination of item content and factor

structure. PLoS One. 2013;8(3):e58067. https://doi.org/10.1371/journal.pone.0058067.
16. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS). Recent evidence and development of a shorter version. In: Brink TL, editor. Clinical gerontology: a guide to assessment and intervention. NY: The Haworth Press, Inc.; 1986. p. 165–73.
17. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
18. Park Y, Jung JY, Kim YS, Chung KS, Song JH, Kim SY, Kim EY, Kang YA, Park MS, Chang J, Leem AY. Relationship between depression and lung function in the general population in Korea: a retrospective cross-sectional study. Int J Chronic Obstruct Pulmonary Dis. 2018;13:2207–13. https://doi.org/10.2147/COPD.S169025.
19. Kubzansky LD, Sparrow D, Jackson B, et al. Angry breathing: a prospective study of hostility and lung function in the Normative Aging Study. Thorax. 2006;61:863–8.
20. Swigris JJ, Esser D, Conoscenti CS, Brown KK. The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review. Health Qual Life Outcomes. 2014;12(1):124.
21. Windisch W, Freidel K, Schucher B, et al. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. J Clin Epidemiol. 2003;56(8):752–9.
22. Vidotto G, Carone M, Jones PW, Salini S, Bertolotti G. Maugeri respiratory failure questionnaire reduced form: a method for improving the questionnaire using the Rasch model. Disabil Rehab. 2007;29(13):991–8.
23. Balestroni G, Bertolotti G. EuroQol-5D (EQ-5D): an instrument for measuring quality of life. Monaldi Arch Chest Dis. 2012;78:155–9.
24. Munari AB, Gulart AA, dos Santos K, Venâncio RS, Karloh M, Mayer AF. Modified medical research council dyspnea scale in GOLD classification better reflects physical activities of daily living. Respir Care. 2018;63(1):77–85. https://doi.org/10.4187/respcare.05636.
25. Oga T, Taniguchi H, Kita H, Tsuboi T, Tomii K, Ando M, Kojima E, Tomioka H, Taguchi Y, Kaji Y, Maekura R, Hiraga T, Sakai N, Kimura T, Mishima M, Windisch W, Chin K. Comparison of different disease-specific health-related quality of life measurements in patients with long-term noninvasive ventilation. Can Respir J. 2017;2017:8295079., 7 pages. https://doi.org/10.1155/2017/8295079.
26. Oga T, Taniguchi H, Kita H, Tsuboi T, Tomii K, Ando M, Kojima E, Tomioka H, Taguchi Y, Kaji Y, Maekura R, Hiraga T, Sakai N, Kimura T, Mishima M, Chin K. Analysis of the relationship between health status and mortality in hypercapnic patients with noninvasive ventilation. Clin Respir J. 2017;11:772–80. https://doi.org/10.1111/crj.12415.
27. Andreou G, Vlachos F, Makanikas K. Effects of chronic obstructive pulmonary disease and obstructive sleep apnea on cognitive functions: evidence for a common nature. Sleep Disord. 2014;2014:768210.
28. Thakur N, Blanc PD, Julian LJ, et al. COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. Int J Chron Obstruct Pulmon Dis. 2010;5:263–9.
29. Zheng GQ, Wang Y, Wang XT. Chronic hypoxiahypercapnia influences cognitive function: a possible new model of cognitive dysfunction in chronic obstructive pulmonary disease. Med Hypotheses. 2008;71:111–3.
30. Liesker JJ, Postma DS, Beukema RJ, et al. Cognitive performance in patients with COPD. Respir Med. 2004;98:351–6.
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
32. Mioshi E, Dawson K, Mitchell J, et al. The Addenbrooke's Cognitive' Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry. 2006;21:1078–85.
33. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
34. Agrell B, Dehlin O. The clock-drawing test. Age Ageing. 1998;27:399–403.
35. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256:183–94.
36. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology. 2000;55(11):1621–6.
37. Campbell GB, Whyte EM, Sereika SM, Dew MA, Reynolds CF 3rd, Butters MA. Reliability and validity of the Executive Interview (EXIT) and Quick EXIT among community dwelling older adults. Am J Geriatric Psychiatry. 2014;22(12):1444–51. https://doi.org/10.1016/j.jagp.2013.08.009.
38. Wilson JE, Mart MF, Cunningham C, et al. Delirium Nat Rev Dis Primers. 2020;6:90. https://doi.org/10.1038/s41572-020-00223-4.
39. European Delirium Association* and American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer European Delirium Association. BMC Med. 2014;12:141.
40. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. Ann Intern Med. 1990;113(12):941–8.
41. Funk GC, Schmerz U. Delir bei akuter respiratorischer Insuffizienz [Pain, agitation and delirium in acute respiratory failure]. Med Klin Intensivmed Notfmed. 2016;111(1):29–36. https://doi.org/10.1007/s00063-015-0136-6. German, Epub 2016 Jan 27
42. Borgmann M, Ivanda M, Hadizamani Y, Mohaupt M, Bals R, Lucas R, et al. Short report: does the 6-minute walk test in hospitalized COPD patients exclusively

correlate with lung function parameters or should psychological factors also be taken into account? PLoS One. 2020;15(5):e0232587. https://doi.org/10.1371/journal.pone.0232587.
43. Phillips D, Pagnini F. A mindful approach to chronic illness. In: Le IA, Ngnoumen CT, Langer E, editors. The Wiley Blackwell handbook of mindfulness. London: Wiley-Blackwell; 2014. p. 852–63.
44. Vrijsen B, Chatwin M, Contal O, Derom E, Janssens JP, Kampelmacher MJ, Muir JF, Pinto S, Rabec C, Ramsay M, Randerath WJ, Storre JH, Wijkstra PJ, Windisch W, Testelmans D. Hot topics in non-invasive ventilation: report of a Working Group at the International Symposium on Sleep-Disordered Breathing in Leuven. Belgium Respir Care. 2015;60(9):1337–62.
45. Scala R, Pisani L. Noninvasive ventilation in acute respiratory failure: which recipe for success? Eur Respir Rev. 2018;27(149):180029.
46. Santoni G, Marengoni A, Calderón-Larrañaga A, Angleman S, Rizzuto D, Welmer AK, Mangialasche F, Orsini N, Fratiglioni L. Defining health trajectories in older adults with five clinical indicators. J Gerontol A Biol Sci Med Sci. 2017;72(8):1123–9.
47. Ritz T. Airway responsiveness to psychological processes in asthma and health. Front Physiol. 2012;3:343. https://doi.org/10.3389/fphys.2012.00343.
48. Balkrishnan R, Christensen DB. Inhaled corticosteroid use and associated outcomes in elderly patients with moderate to severe chronic pulmonary disease. Clin Ther. 2000;22:452–69.
49. Volpato E, Pagnini F, Banfi P. The implementation of a psychological support during the adaptation to Non Invasive Ventilation (NIV) in Chronic Obstructive Pulmonary Disease (COPD): a Randomized Controlled Trial. Eur Respir J. 2018;52(Suppl 62):OA5409. https://doi.org/10.1183/13993003.congress-2018.OA5409.

Part VII

Noninvasive Ventilation: Pulmonary Function Testing Guidelines

46 Evidence-Based Recommendations for Pulmonary Function Measurement and Outcomes

Mehmet Selim Comez and Antonio M. Esquinas

Abstract

The pulmonary function test is most often performed by a spirometer. It is important to provide objective information in monitoring lung health and recognizing pulmonary diseases. To this end, some standardizing guidelines have been published since 1979. The guideline, which was updated jointly by ATS and ERS in 2019, offers standards and common recommendations to manufacturers, clinicians, operators, and researchers.

Keywords

Pulmonary function test · Spirometry · Practice guideline · Lung volume measurements

Abbreviations

ATS	American Thoracic Society
BEV	Back-extrapolated volume
EOFE	End of forced expiration
EOT	End of test
ERS	European Respiratory Society
FET	Forced expiratory time
FEV	Forced expiratory volume
FIVC	Forced inspiratory vital capacity
FVC	Forced vital capacity
GLI	The Global Lung Initiative
IC	Inspiratory capacity
PEF	Peak expiratory flow
TLC	Total lung capacity
VC	Vital capacity

46.1 Introduction

Pulmonary function tests are most commonly performed by spirometry. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) accepted technical standards for spirometry testing in 2005. Later, the evidence-based guideline for spirometry was updated by ATS and ERS in 2019. The 2005 standards were revised in this guide, including additional factors not having been previously considered. Additional standards in the last update have been

M. S. Comez (✉)
Anesthesiology and Reanimation Department, Tayfur Ata Sökmen Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey

A. M. Esquinas
Intensive Care Unit, Hospital General Universitario Morales Meseguer, Murcia, Spain

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

A. M. Esquinas (ed.), *Pulmonary Function Measurement in Noninvasive Ventilatory Support*,
https://doi.org/10.1007/978-3-030-76197-4_46

improved for occupational observation and preschool children. In general, the 2019 guideline includes descriptions, equipment specifications, quality control, patient-related processes, and data reporting. These standards are the minimum criteria that must be fulfilled for the spirometry test [1].

The recommendations in the 2019 guideline represent a consensus of task force members on available evidence for various aspects of spirometric measurement, and otherwise reflects the expert opinion of the task force members for areas where peer-reviewed evidence is not available or missing. The term "must" used in the guideline is used to state a necessity to meet standards, and the term "should" is used to state activities that may not be mandatory but are contemplated to be best applications [1].

46.2 Discussion and Analysis of the Main Topics

46.2.1 The 2019 Guideline for Spirometry

46.2.1.1 The Patient Experience

Patients stated the need for more information concerning spirometry prior to the test in a survey conducted by the European Lung Foundation [1].

46.2.1.2 Indications

Spirometry allows to measure the impact of the disease on lung function, to evaluate airway responsiveness, to monitor the outcome of therapeutic interventions or disease course, to assess preoperative risk, and to determine a prognosis for many respiratory conditions [1].

46.2.1.3 Relative Contraindications

Intrathoracic, intraabdominal, and intracranial pressures may increase during the forced expiratory maneuver used in spirometry [1, 2]. Potential risks of forced expiratory maneuver are mainly associated with maximum pressures produced in the thorax and their effects on intraabdominal and intrathoracic organs, venous return and systemic blood pressure, and expansion of the chest wall and lung. In addition, the physical effort required for maneuvering can raise the oxygen demand of myocardium. Caution must be exercised for patients with medical circumstances that may be adversely influenced by these physiological outcomes (Table 46.1). The potential risks related to testing should all the time be weighed against the advantage of learning about pulmonary function. If the patient feels pain during maneuvering, spirometry should be stopped [1, 3].

46.2.1.4 Laboratory Details

The temperature and pressure of the medium and the time of day must be recorded. Tests should preferably be carried out in a quiet and comfort-

Table 46.1 Relative contraindications for spirometry (based on data from 1)

1. Due to increases in myocardial demand or changes in blood pressure
a. Acute myocardial infarction within 1 week
b. Systemic hypotension or severe hypertension
c. Significant atrial/ventricular arrhythmia
d. Noncompensated heart failure
e. Uncontrolled pulmonary hypertension
f. Acute cor pulmonale
g. Clinically unstable pulmonary embolism
h. History of syncope related to forced expiration/cough
2. Due to increases in intracranial/intraocular pressure
a. Cerebral aneurysm
b. Brain surgery within 4 weeks
c. Recent concussion with continuing symptoms
d. Eye surgery within 1 week
3. Due to increases in sinus and middle ear pressures
a. Sinus surgery or middle ear surgery or infection within 1 week
4. Due to increases in intrathoracic and intraabdominal pressure
a. Presence of pneumothorax
b. Thoracic surgery within 4 week
c. Abdominal surgery within 4 week
d. Late-term pregnancy
5. Infection control issues
a. Active or suspected transmissible respiratory or systemic infection, including tuberculosis
b. Physical conditions predisposing to transmission of infections, such as hemoptysis, significant secretions, or oral lesions or oral bleeding

able environment. Drinking water should be present. Tissues or paper towels should be provided to help patients cope with secretions. The patient should sit upright, shoulders lightly back and jaw lightly raised. A chair with arms, with a height adjustment, and without wheels should be used to prevent the patient's fall. A smaller chair or a raised footstool should be ensured for children and small adults. A noseclip or manual plugging of the nostrils should be used for the maneuvers. If testing is performed while the patient is in another position, this must be documented in the report [1].

46.2.1.5 Hygiene and Infection Control

The operator must wash their hands or use an approved hand sanitizer prior to touching the patient [4]. The patient should be given hand disinfectant after the first entrance into the test station [1].

Whole disposable products, including mouthpieces, nose clips, gloves, and filters, must be discarded at the end of the test. Hands must be washed immediately following direct transport of mouthpieces, tubes, breathing valves, or internal spirometry surfaces to prevent operator exposure and cross-contamination. Gloves should be dressed when touching potentially contaminated equipment and/or if the operator has open cuts or wounds. Manufacturers must clearly define admissible methods for cleaning and disinfecting their equipment, including recommended chemicals and concentrations, as well as protective measures for the operator [1, 3].

Extra measures should be taken for patients with or suspected contagious diseases. Possible measures include testing equipment only for infected patients or testing these patients at the end of the working day and/or testing patients in their own rooms with sufficient air conditioning and proper precaution for the operator [1, 5].

46.2.1.6 Equipment

Manufacturers must secure that all spirometers meet the standards covered in the current ISO 26782 update [1, 3, 6]. Regardless of performance requirements, within ±3.0% for accuracy, linearity, and repeatability adopted in the ISO 26782, the 2005 guideline [3], spirometric equipment must have a maximum allowable error of ±2.5% when testing with a 3-L calibration syringe and using ISO 26782 test profiles. In order to digitize the flow or volume signal, the sampling rate must be>100 Hz with a resolution of at least 12 bits [1].

Both volume-time and flow-volume real-time monitors are required for optimum quality control. Operators must visually inspect each maneuver's performance for quality guarantee prior to moving on to another maneuver. For the flow–volume graph, expiratory flow must be drawn upward and expiratory volume to the right. A 2:1 aspect ratio must be maintained between flow and volume scales. At the beginning of test display, the volume–time graph must start at the maximum inspiration point or 1 second prior to Time 0, whichever comes first. The display of the maneuver should proceed until the end of the plateau or the onset of inspiration [1, 3].

Ambient barometric pressure, saturated water vapor, and body temperature must be presented in all spirometry outcomes. The ambient temperature must be enrolled with an accuracy of ±1 °C. Operators should have notice of possible issues with tests done outside the range of ambient temperatures and barometric pressures specified by the manufacturer for their specific spirometers. Changes in spirometer or flow sensor temperature can be a cause of variability. The spirometer temperature should be measured and should not be supposed to be stable even during a test session. The temperature inside the spirometer should be measured for every respiration maneuver, when using a volume spirometer [1, 3].

46.2.1.7 Device Quality Assurance

The minimum requirements for equipment quality assurance and calibration are as follows: *(1) maintenance of a log of calibration results, (2) documentation of repairs or other alterations that return the equipment to acceptable operation, (3) recording of dates of computer software and hardware updates or changes, and (4) recording the dates equipment is changed or*

Table 46.2 Equipment quality assurance (for both volume- and flow-based sensors); based on data from 1

1. Spirometer
a. Daily calibration verification at low, medium, and high flows: If the calibration verification fails, check for and remediate problems and repeat calibration verification.
b. If an in-line filter is used in spirometry testing, then it must also be used during recalibrations and verifications.
c. Recalibrate the spirometer both after failed calibration verification and at intervals specified by the manufacturer.
d. If the change in calibration factor is ≥6% or varies by more than ±2 SD from the mean, inspect and, if necessary, clean the spirometer according to the manufacturer's instructions; check for errors and recalibrate the spirometer.
e. Perform routine checks and maintenance at intervals specified by the manufacturer**.**
2. 3-L calibration syringe
a. Daily inspection for displacement of the piston stop.
b. Daily check for smooth operation of the syringe with no sticking or catching.
c. Accuracy of ± 0.015 L verified by manufacturer on delivery and at intervals recommended by the manufacturer.
d. Monthly syringe leak test.
3. Documentation
a. A log of all quality control findings, repairs and adjustments, and hardware and software updates.
b. Verification of reference value calculations after software updates.

relocated. Calibration verifications and quality control procedures must be repeated after any such changes before further testing begins [1]. The main aspects of equipment quality guarantee are summarized in Table 46.2.

The spirometry system must determine the zero flow level by blocking the spirometer before calibration, calibration verifications, and patient tests. Spirometer calibration verifications must be done at least daily by using a 3-L syringe cycled at least three times to provide a range of flows varying between 0.5 and 12 L/s (with 3-L injection times between 0.5 and 6 s). The volume at each flow must meet the accuracy requirement of ±3% (±2.5% for spirometers plus ±0.5% for calibration syringes) for both inspiration and expiration (or for expiration only for volume-based spirometers) [1].

46.2.1.8 Operator Details

Operator training, competence acquisition, and maintenance must be integrated in any spirometry testing service [1]. In addition, changes in the 2019 guideline include requirements for operator comments and the spirometry system to provide feedback to the operator.

46.2.1.9 Patient Details

It must be recorded age in years, height in centimeters, and weight in kg (up to the nearest 0.5 kg) to one decimal place. Body mass index should be calculated in kg/m2. Height must be measured without shoes, feet together, standing as tall as possible at eye level and looking straight ahead, and leaning against the back wall or stadiometer. For patients who cannot stand upright, height may be predicted using the ulna length or arm span, being aware that there are gender, age, and ethnic differences in such predictions [1, 3].

Gender and ethnicity should be included in patient information regarding spirometry demand. If gender and/or ethnicity data are not revealed, operator annotations must warn the interpreter about this negligence and indicate which default values are used to calculate the predicted values [1, 3].

Patients should avoid the activities listed in Table 46.3 prior to testing, and these demands should be given to the patient when making the appointment. All these manners must be checked, and all deviations must be enrolled before the spirometry test. Patients should be as comfort-

Table 46.3 Activities that should be avoided before lung function testing (based on data from 1)

1. Smoking and/or vaping and/or water pipe use within 1 h before testing (to avoid acute bronchoconstriction due to smoke inhalation)
2. Consuming intoxicants within 8 h before testing (to avoid problems in coordination, comprehension, and physical ability)
3. Performing vigorous exercise within 1 h before testing (to avoid potential exercise-induced bronchoconstriction)
4. Wearing clothing that substantially restricts full chest and abdominal expansion (to avoid external restrictions on lung function)

able as possible prior to and pending the tests. Patients should be requested to loosen their tight-fitting clothing [1, 3].

Instructions on drugs that should be discontinued should be given to the patient at the time of appointment. The operator must enroll the type and dosage of drugs that may change pulmonary function and when the drugs were last taken. The operator should declare viewed signs or symptoms such as coughing, wheezing, dyspnea, or cyanosis [1, 3].

46.2.1.10 Forced Expiratory Volume, First second (FEV1) and Forced Vital Capacity (FVC) Maneuver

Test Procedure: The main measurements are FEV1 and FVC. There are four different stage of the FVC maneuver for spirometers that measure expiration and inspiration: *(1) maximal inspiration, (2) a "blast" of expiration, (3) continued complete expiration for a maximum of 15 s* (the spirometry must signal the operator when a plateau is arrived or forced expiratory time (FET) arrives 15th second), *and (4) inspiration at maximal flow back to maximum lung volume* [1].

The operator must demonstrate the proper technique and follow the procedure defined in Table 46.4. In some cases, such as patients with tracheostomy or nasal resection, noninvasive regulations (sealing face mask, tubing connectors, or occlusion valves, etc.) can be implemented at and must be enrolled in the operator's annotations [1].

Operators participating in the pulmonary function test of young children should be specially trained and able to work with this population [1, 7].

Within-Maneuver Evaluation: The 2019 update spirometry standards focus on the acceptability of individual FEV1 and FVC measurements rather than maneuver as a whole. New standards include new objective methods to establish which FEV1 and FVC measurements are acceptable and which technically unacceptable measurements could still be of clinical utility (Table 46.5) [1].

Table 46.4 Procedures for FVC maneuvers (based on data from 1)

1. **Wash hands** (or use an approved hand sanitizer)
2. **Prepare the patient**
a. Dispense hand sanitizer for the patient
b. Confirm patient identification, age, birth sex, ethnicity, etc.
c. Measure weight and height without shoes
d. Ask about activities listed in Table 46.3, medication use, and any relative contraindications flagged on the requisition; note respiratory symptoms
3. **Instruct and demonstrate the test**
a. Position of the mouthpiece and noseclip
b. Correct posture with head slightly elevated
c. Inspire rapidly until completely full
d. Expire with maximal effort until completely empty
e. Inspire with maximal effort until completely full
f. Confirm that patient understands the instructions and is willing to comply
4. Perform maneuver
a. Have patient assume the correct posture
b. Attach noseclip, place mouthpiece in mouth, and close lips around the mouthpiece
c. Breathe normally
d. Inspire completely and rapidly with a pause of ≤ 2 s at TLC
e. Expire with maximal effort until no more air can be expelled while maintaining an upright posture
f. Inspire with maximal effort until completely full
g. Repeat instructions as necessary, coaching vigorously
h. Repeat for a minimum of three maneuvers, usually no more than eight for adults
i. Check FEV1 and FVC repeatability and perform more maneuvers as necessary
5. Perform maneuver (expiration-only devices)
a. Have patient assume the correct posture
b. Attach noseclip
c. Inspire completely and rapidly with a pause of ≤ 2 s at TLC
d. Place mouthpiece in mouth and close lips around the mouthpiece
e. Expire with maximal effort until no more air can be expelled while maintaining an upright posture
f. Repeat instructions as necessary, coaching vigorously
g. Repeat for a minimum of three maneuvers, usually no more than eight for adults
h. Check FEV1 and FVC repeatability and perform more maneuvers as necessary

The onset of forced expiration is determined by the back-extrapolated method for timing purposes [1, 3, 6]. *The back-extrapolated volume (BEV) is the volume of gas that has been expired*

Table 46.5 Summary of acceptability, usability, and repeatability criteria for FEV1 and FVC (based on data from 1)

Acceptability and usability criteria	Required for acceptability		Required for usability	
	FEV1	FVC	FEV1	FVC
Must have BEV ≤ 5% of FVC or 0.100 L, whichever is greater	Yes	Yes	Yes	Yes
Must have no evidence of a faulty zero-flow setting	Yes	Yes	Yes	Yes
Must have no cough in the first second of expiration (Age ≤ 6 yr.: 0.75 s)	Yes	No	Yes	No
Must have no glottic closure in the first second of expiration (Age ≤ 6 yr.: 0.75 s)	Yes	Yes	Yes	Yes
Must have no glottic closure after 1 s of expiration	No	Yes	No	No
Must achieve one of these three EOFE indicators: 1. Expiratory plateau (≤0.025 L in the last 1 s of expiration) 2. Expiratory time ≥ 15 s 3. FVC is within the repeatability tolerance of or is greater than the largest prior observed FVC	No	Yes	No	No
Must have no evidence of obstructed mouthpiece or spirometer	Yes	Yes	No	No
Must have no evidence of a leak	Yes	Yes	No	No
If the maximal inspiration after EOFE is greater than FVC, then FIVC-FVC must be ≤0.100 L or 5% of FVC, whichever is greater	Yes	Yes	No	No
Repeatability criteria (applied to acceptable FVC and FEV1 values) Age > 6 yr.: The difference between the two largest FVC values must be ≤ 0.150 L, and the difference between the two largest FEV1 values must be ≤ 0.150 L Age ≤ 6 yr.: The difference between the two largest FVC values must be ≤ 0.100 L or 10% of the highest value, whichever is greater, and the difference between the two largest FEV1 values must be ≤ 0.100 L or 10% of the highest value, whichever is greater				

BEV back-extrapolated volume, *EOFE* end of forced expiration, *FEV0.75* forced expiratory volume in the first 0.75 s, *FIVC* forced inspiratory VC

from maximal lung volume to Time 0 and is included in the FEV1 and FVC measurements [1]. To obtain a right Time 0 and provide that the FEV1 comes from a maximum effort, the BEV, whichever is greater, must be <5% of the FVC or 0.100 L [1, 8].

End of forced expiration (EOFE) is essential for achieving a true FVC. It is necessary to reach one of the following three recommended EOFE indicators:

1. *There is less than a 0.025-L change in volume for at least 1 s (a "plateau")* (the most dependable sign). The spirometry system must ensure both a sign on the real-time display and an audible warning (a single beep) when this criterion is achieved [1].
2. *The patient has achieved an FET of 15 s.* The spirometry system must ensure both a sign on the real-time display and an audible warning (a single beep) when this criterion is achieved [1].
3. If the patient cannot expire long enough to achieve a plateau (restrictive lung disease, etc.), the measure of whether EOFE is reached is whether the patient has again and again attained the same FVC. *For within maneuver acceptability, the FVC must be greater than, or within the repeatability tolerance of, the largest FVC observed before this maneuver in the current testing set* [1].

Maneuvers that do not fulfill any of the EOFE acceptability criteria will not ensure acceptable FVC measures. If the maximum inspiratory volume (FIVC) after EOFE is greater than FVC, it indicates that the patient has not started maneuver from TLC (Total Lung Capacity). FEV1 and FVC measurements from a maneuver with FIVC-FVC > 0.100 L or 5% of FVC, whichever is greater, are unacceptable [1].

There must be no leakage in the mouth during the maneuver [8]. In the first second of the maneuver, cough can affect the measured FEV1 value, and from this maneuver, FEV1 is neither acceptable nor usable. However, FVC may be acceptable. Glottic closing or early finish, such as inspiration or get out of the mouthpiece, makes FVC unacceptable and, if it happens during the

first 1 s, makes FEV1 unacceptable and unusable. A similar finish during the first 0.75 s makes FEV0.75 unacceptable and unusable [1].

The spirometry must provide to the operator clear feedback showing FEV1 and FVC acceptability at the finish of each maneuver. The operator must have the capability to run over the acceptability assignment because the operator may notice a leak, cough, insufficient inspiration or expiration, or an incorrect zero flow level not perceived by the software. Records of all maneuvers that include acceptable or usable FEV1 and / or FVC must be kept since for some patients; their best performance may only provide usable data that do not fulfill the acceptability criteria [1].

Between-Maneuver Evaluation: The aim of each prebronchodilator test set and postbronchodilator test set is to obtain at least three acceptable FEV1 and three acceptable FVC measurements. Acceptable FEV1 and FVC measurements are not mandatory to be performed from the same maneuver. The operator must ensure that the patient has sufficient time to recover between maneuvers and agree to do another maximum maneuver. FVC repeatability is accomplished when the difference between the largest and the next largest FVC for patients older than 6 years is ≤0.150 L and for those 6 years and younger, whichever is greater, ≤0.100 L or 10% of the largest FVC [1, 7]. FEV1 repeatability is accomplished when the difference between the largest and the next largest FVC for patients older than 6 years is ≤0.150 L and for those 6 years and younger, whichever is greater, ≤0.100 L or 10% of the largest FEV1. If these criteria are not fulfilled in three maneuvers, up to eight maneuvers must be attempted in adults. If the FEV1 from an acceptable test falls below 80% of the beginning value, the test procedure should be discontinued for patient safety. While testing children, more than eight attempts may be required as not every attempt may be a complete maneuver [1].

46.2.1.11 Bronchodilator Responsiveness Testing

The bronchodilator responsiveness test is the measurement of the degree of recovery of air flow in response to bronchodilator administration with changes in FEV1 and FVC. Since normal baseline spirometry does not rule out the bronchodilator response, the first spirometry should be performed both before and after bronchodilator administration. Recommended withholding times for various bronchodilators are listed in Table 46.6. Inhaled corticosteroids and leukotriene modifiers do not need to be withheld [1].

Table 46.6 Bronchodilator withholding times (based on data from 1)

Bronchodilator medication	Withholding times
SABA (e.g., albuterol or salbutamol)	4–6 h
SAMA (e.g., ipratropium bromide)	12 h
LABA (e.g., formoterol or salmeterol)	24 h
Ultra-LABA (e.g., indacaterol, vilanterol, or olodaterol)	36 h
LAMA (e.g., tiotropium, umeclidinium, aclidinium, or glycopyrronium)	36–48 h

LABA long-acting b2-agonist, *LAMA* long-acting muscarinic antagonist, *SABA* short-acting b2-agonist, *SAMA* short-acting muscarinic antagonist

Note: In the case of dual bronchodilators, the withholding time for the longer-acting bronchodilator is used

Each facility that performs a bronchodilator response test must have a written protocol for the test. Spirometry must allow the operator to change the assignment of the maneuver from prebronchodilator to postbronchodilator, and vice versa. When the first postbronchodilator maneuver is performed by the operator, spirometry must show the time elapsed since the last prebronchodilator maneuver. If the elapsed time is less than the waiting time for the bronchodilator effect, spirometry must give the operator a cautionary message [1].

46.2.1.12 Reported Values

The variables measured in spirometry are FVC, FEV1, FEV1/FVC, PEF (peak expiratory flow), FET, FIVC, and FEV0.75, FEV0.75/FVC (for children 6 years and under). Spirometry systems must be able to measure and report these variables as recommended in the ATS standardized format [1, 9]. The measurements are reported separately for the sets of prebronchodilator and postbronchodilator maneuvers. The measurements are recorded separately for the prebronchodilator and postbronchodilator maneuver sets.

Table 46.7 Grading system for FEV1 and FVC (graded separately) (based on data from 1 and 9)

Grade	Number of measurements	Repeatability: age > 6 yr.	Repeatability: age ≤ 6 yr.[a]
A	≥3 acceptable	Within 0.150 L	Within 0.100 L[a]
B	2 acceptable	Within 0.150 L	Within 0.100 L[a]
C	≥2 acceptable	Within 0.200 L	Within 0.150 L[a]
D	≥2 acceptable	Within 0.250 L	Within 0.200 L[a]
E	≥2 acceptable	> 0.250 L	> 0.200 L[a]
	or 1 acceptable	N/A	N/A
U	0 acceptable and ≥ 1 usable	N/A	N/A
F	0 acceptable and 0 usable	N/A	N/A

N/A not applicable
Note 1: The repeatability grade is determined for the set of prebronchodilator maneuvers and the set of postbronchodilator maneuvers separately. The repeatability criteria are applied to the differences between the two largest FVC values and the two largest FEV1 values. Grade U indicates that only usable but not acceptable measurements were obtained
[a]Or 10% of the highest value, whichever is greater; applies for age 6 years or younger only

In patients with airflow obstruction, the FVC may rely on FET. The interpreter must be aware that a marked change in FVC following bronchodilator administration may depend on a change in FET [1].

The ATS/ERS states that FEV0.75 and FEV0.5 should also be reported in the respiratory function test in preschool children [7]. If FET is >1 s, FEV1 should also be reported [10].

The ATS standard report form [9] should be the default report form for spirometry. The set of default reference values for all ages should be reference equations of The Global Lung Function Initiative (GLI) [10]. Apart from the outline reports, the interpreter should have access to a report of all maneuvers within a test session. The flow and/or volume data must be available for the facility manager to obtain outcomes and plot volume-time and flow-volume charts. The system should also be able to transfer data to electronic medical records. Names and codes should be used to identify test data. The date and time must be recorded for each maneuver (to confirm pre- and post-bronchodilator maneuvers and diurnal variations) [1].

The system must allow the operator to enter interpretations from the drop-down menu as well as free text. The facility manager should be capable to direct the list of menu options [1].

46.2.1.13 Grading the Quality of the Test Session

The grading system recommended by ATS for spirometry reporting [9] should be used (Table 46.7). This system informs the interpreter about the level of trust. FEV1 and FVC are graded separately. While some maneuvers may be usable or acceptable at grade levels lower than A, the operator's primary aim must always be to reach the best possible test quality for every patient [1].

46.2.1.14 Vital Capacity (VC) and Inspiratory Capacity (IC) Maneuvers

The spirometry must comply with the necessities of FVC maneuvers for VC and IC measurements. The display of the VC maneuver must cover both inspiratory and expiratory maneuvers. A display of the whole recorded VC maneuver (regardless of the use of inspiratory or expiratory maneuver) must be ensured to determine whether the patient has received a plateau in expiratory effort [1].

46.2.2 The 2019 Updates from the 2005 Guidelines

(a) The previous relative contraindication of testing within one month of myocardial infarction is altered to 1 week [1].
(b) Spirometers are required to meet ISO 26782 standards, with the exception that they must have a maximum permissible error of ±2.5% for accuracy, linearity, and repeatability when tested with a 3-L calibration syringe and using ISO 26782 [1].

(c) The procedures regarding accuracy requirement and calibration verification for device quality assurance have been updated [1].
(d) Operator training and competence acquisition and maintenance must be integrated in any spirometry testing service [1].
(e) The list of activities that patients should refrain prior to testing has been updated [1].
(f) The new standards of FEV1 and FVC maneuver focus on the use of devices that measure both expiration and inspiration, with four different stages to the FVC maneuver: *(1) maximal inspiration; (2) a "blast" of expiration; (3) continued complete expiration for a maximum of 15 s; and (4) inspiration at maximal flow back to maximum lung volume* [1].
(g) The maximum acceptable BEV, whichever is greater, is reduced to ≤5% of the FVC or 0.100 L. The time to increase from 10% to 90% of the peak flow should be ≤150 ms. The term "EOFE" has been replaced with the term "end of test" (EOT) due to the fact that EOFE is not the end of the maneuver. New criteria have been set for an acceptable EOFE. If the maximum inspiratory volume (FIVC) after EOFE is greater than FVC, FEV1 and FVC measurements from a maneuver with FIVC-FVC > 0.100 L or 5% of FVC are unacceptable, whichever is greater. For children ≤6 years old, the difference between the two largest FEV1 values and the two largest FVC values must be ≤0.100 L or 10% of the maximum value, whichever is greater. A standard warning messages table is ensured to alert the operator of possible problems with each maneuver. Criteria are provided to determine whether unacceptable FEV1 and FVC measurements may still be clinically useful [1].
(h) The term bronchodilator responsiveness testing has been replaced with reversibility testing to avoid unwarranted interference. A new table of bronchodilator withholding times is presented. An example procedure is provided for bronchodilator administration by nebulizer. In addition, an updated bronchodilator administration by metered dose inhaler is provided. If the time between the last pre-bronchodilator maneuver and the first post-bronchodilator maneuver is less than the waiting time required to respond to the bronchodilator, the system is required to issue a warning message [1].
(i) The 2017 ATS Recommendations for a Standardized Pulmonary Function Report should be used for grading the quality of the test session [1].
(j) A drop down menu is required for standard operator feedback [1].
(k) The repeatability criterion is changed for VC and IC maneuvers. The VC difference between the biggest and the following biggest maneuver must be ≤0.150 L or 10% VC, whichever is smaller, for>6 years old, and ≤ 0.100 L or 10% VC, whichever is smaller, for ≤6 years [1].

46.3 Conclusion Discussion

Even if the recommended standards are not perfect, they reflect current knowledge in the field. That is why, the updated guidelines should be used as a guide for good clinical practice till changes are made on new scientific evidence. If the PFT done does not meet the standards set in the guide, in that case the reliability of the results will decrease. New research studies, improved quality assurance approaches, and improvements in instrumentation and computer skills require constant revision.

Key Major Recommendations

- Current evidence-based guidelines should be used as a guide for good clinical practice till changes are made on new scientific evidence.
- The healthcare professional should decide the spirometry request on the basis of benefit and harm for the patient.
- In some cases, the acceptability and repeatability criteria of the test may not be met; however, the results may be used clinically.

References

1. Graham BL, Steenbruggen I, et al. Standardization of Spirometry 2019 Update: An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200:e70–88.
2. Tiller NB, Simpson AJ. Effect of spirometry on intrathoracic pressures. BMC Res Notes. 2018;11:110.
3. Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
4. Pittet D, Allegranzi B, Boyce J, World Health Organization World Alliance for Patient Safety First Global Patient Safety Challenge Core Group of Experts. The World Health Organization guidelines on hand hygiene in health care and their consensus recommendations. Infect Control Hosp Epidemiol. 2009;30:611–22.
5. Wanger J, Mottram C. ATS pulmonary function laboratory management and procedure manual. 3rd ed. New York: American Thoracic Society; 2016.
6. International Organization for Standardization. ISO 26782. Anaesthetic and respiratory equipment: spirometers intended for the measurement of time forced expired volumes in humans. Geneva, Switzerland: International Organization for Standardization; 2016.
7. Beydon N, Davis SD, Lombardi E, et al. American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175:1304–45.
8. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med. 1995;152:1107–36.
9. Culver BH, Graham BL, Coates AL, et al. ATS Committee on Proficiency Standards for Pulmonary Function Laboratories. Recommendations for a standardized pulmonary function report: an Official American Thoracic Society technical statement. Am J Respir Crit Care Med. 2017;196:1463–72.
10. Quanjer PH, Stanojevic S, Cole TJ, et al. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the Global Lung Function 2012 equations. Eur Respir J. 2012;40:1324–43.