

Antonio M. Esquinas
Editor

Noninvasive Mechanical Ventilation

Theory, Equipment, and
Clinical Applications

Second Edition

 Springer

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Murcia
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To my wife Rosario

Preface

Despite significant technological advances in medicine today, the reality of everyday practice continues to reveal that not everyone can apply and know the limits of the technologies used in the treatment of respiratory failure.

Nowadays, in the treatment of acute respiratory failure in various medical specialties, the use of noninvasive mechanical ventilation continues to show a positive end result. There are few hospitals that have the necessary equipment to make its implementation possible. However, as we will see in this second edition, there are still several points of controversy, and important advances continue to be made, not only in new indications but also in the equipment (mechanical ventilator, interfaces) and patient–ventilator interaction. This gives scope for improving our understanding and maintains a growing interest in new possibilities.

In this second edition, we have analyzed the impact of published studies on the effects of potential, new noninvasive ventilation treatments and clinical practice, described by well-known researchers as well as other emerging groups of young researchers.

Experience and new insights make this book a basic reference to understanding and encouraging new ideas.

Personally, I want to thank all authors for trusting and contributing their time and efforts in the development of this book. Finally, if I wanted to point out that we must not stop this research inertia on noninvasive mechanical ventilation, knowing communicate well their knowledge and limits, and never forget that our end reference points problems and circumstances that our patients during noninvasive mechanical ventilation raising to us day to day.

This technique is still a life-saving treatment, relieves pain for many patients, and gives encouragement. However, many aspects need to be reinvestigated and research is necessary to resolve open controversies which indicate the failures of noninvasive ventilation, methodology, and therapy. The question of what are the limits of noninvasive ventilation and where needs to be addressed.

As *Albert Einstein* said, “We cannot solve our problems with the same thinking we used when we created them.” We hope that this second edition becomes a useful reference that serves this modest reflection.

Murcia, Spain

Antonio M. Esquinas, MD, PhD, FCCP

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Part I

Rational, Interface, Equipment and Ventilatory Modes of Non Invasive Mechanical Ventilation

Nicolino Ambrosino

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1.1 Stable Hypercapnic Chronic Obstructive Pulmonary Disease

The hypothesized but not proven mechanisms of action of long-term noninvasive positive pressure ventilation (NPPV) in stable hypercapnic patients with chronic obstructive pulmonary disease (COPD) are

1. Reverting hypoventilation
2. Respiratory muscle unloading
3. Respiratory center reset
4. Cardiovascular effects

These mechanisms may work alone or in synergy.

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1.1.1 Correction of Hypoventilation

Physiological studies have shown that, in stable hypercapnic COPD patients, NPPV in pressure support mode is able to improve alveolar ventilation by increasing the tidal volume and reducing the respiratory rate [1].

1.1.2 Respiratory Muscle Unloading

There is evidence that noninvasive inspiratory pressure is able to unload the inspiratory muscles, whereas the application of positive end-expiratory pressure (PEEP) counteracts the intrinsic PEEP (PEEPi) associated with hyperinflation in these patients [2], an effect more evident in acute exacerbations.

1.1.3 Reset of the Respiratory Centers

There is evidence that, compared with long-term oxygen therapy (LTOT) alone, addition of NPPV at night resulted in significant improvements in daytime arterial oxygen (PaO_2) and carbon dioxide (PaCO_2) tension, total sleep time, sleep efficiency, and overnight PaCO_2 . Quality of life with LTOT plus NPPV was significantly better than with LTOT alone. The degree of improvement in daytime PaCO_2 was significantly correlated with an improvement in mean overnight PaCO_2 [3].

1.1.4 Cardiovascular Effects

Night-time NPPV applied over 3 months may improve heart rate variability, reduce circulating natriuretic peptide levels, and enhance the functional performance of patients with advanced but stable COPD, suggesting that nocturnal NPPV may reduce the impact of cardiac comorbidities in COPD patients [4].

1.2 Acute COPD Exacerbations

In acute exacerbations of COPD leading to acute respiratory failure (ARF), the work of breathing (WOB) is increased as a result of the increase in airway resistances. Because of lung hyperinflation, the respiratory muscles are less effective and, if the underlying pathology does not reverse in a relatively short time, they are at risk of failure and fatigue. Despite an increase in respiratory drive, rapid shallow breathing may lead to reduction in alveolar ventilation, even when minute ventilation is normal or even increased. Respiratory muscles progressively become unable to maintain

adequate alveolar ventilation, resulting in an increase of PaCO₂. When PaCO₂ is severely increased for a prolonged time, the level of consciousness is generally impaired.

1.3 How Does NPPV Work in Acute Exacerbations of COPD?

When the cause of ARF is reversible, medical treatment works to maximize lung function and reverse the precipitating cause, whereas the aim of ventilatory support is [5]

- To buy time for the treatment of the cause of ARF to work
- To decrease the work of breathing (WOB)
- To reverse life-threatening hypoxemia and respiratory acidosis

In these circumstances, inspiratory support works to increase alveolar ventilation by increasing tidal volume and to unload inspiratory muscles by decreasing WOB. The addition of an external PEEP may further reduce WOB by counterbalancing the PEEPi.

Such patients may require intubation for airway protection in addition to ventilatory assistance, unless the hypercapnia can be reversed within minutes. It has been shown that NPPV may avoid most of the complications associated with invasive mechanical ventilation, ensuring at the same time a similar degree of efficacy [6]. The early use of NPPV in COPD patients may prevent further deterioration and thus avoid endotracheal intubation, improving survival compared with standard medical therapy. As a consequence, NPPV is considered as the first-line treatment of acute exacerbations of COPD.

The early use of NPPV is mandatory because success rate decreases with disease progression. On the other hand, NPPV may be useless or even a problem for the patient when applied in mild exacerbations that can be treated only by medical therapy [7]. In other words, as in other fields of medicine, this therapeutic tool should be applied during a therapeutic window: not too early, not too late. In practice, arterial blood gases, and signs (tachypnea or increased accessory muscle use) and symptoms (dyspnea) of increased WOB should be used as markers to start NPPV in these conditions [8]. When NPPV is started early, those patients not in danger (pH not lower than 7.30) can be managed outside of the intensive care unit (ICU), eventually even in a ward with an adequately skilled team [9]. In addition, dedicated units such as high-dependency respiratory intensive care should be encouraged to deliver NPPV to most but not all patients. For these patients, these units may offer noninvasive monitoring systems and higher nurse-to-patient ratios than in general wards with less burden but similar success rates as in ICUs [10].

Key Points

- Possible mechanisms of action of long-term NPPV in stable hypercapnic COPD patients are correction of hypoventilation, respiratory muscle unloading, reset of the respiratory centers, and inducing positive cardiovascular effects.
- The goals of ventilatory support in ARF are to buy time for the treatment of the cause of ARF to work, to decrease the WOB, and to reverse life-threatening hypoxemia and respiratory acidosis.
- NPPV may avoid most of complications associated with invasive mechanical ventilation, ensuring at the same time a similar degree of efficacy.
- NPPV in acute COPD exacerbation must be applied during an appropriate therapeutic window.
- The location of NPPV must be related to timing and severity of disease.

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Cardiopulmonary Function Interactions during Noninvasive Mechanical Ventilation: Key Topics and Clinical Implications

2

Angelo Petroianni

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Abbreviations

CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
FRC	Functional residual volume
ITP	Intrathoracic pressure
LV	Left ventricle
MV	Mechanical ventilation
NIV	Noninvasive ventilation
P_A	Alveolar pressure
P_a	Arterial pressure
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
P_{pl}	Pleural pressure

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PPV	Positive pressure ventilation
P_{tm}	Transmural pressure
P_v	Venous pressure
PVR	Pulmonary vascular resistance
RV	Right ventricle
TLC	Total lung capacity
V/Q	Ventilation/perfusion ratio
VI	Ventricular interdependence
WOB	Work of breathing

2.1 Introduction

The thoracic cavity contains the lungs, with pulmonary vasculature divided into intra- and extra-alveolar vessels, and the heart, with the great veins and thoracic aorta. The dynamic mechanical properties of the thoracic organs are variable and conditioned by their volume and elasticity. Changes in lung volume and pleural pressure (P_{pl}) influence cardiac function even during spontaneous breathing.

The intrathoracic cardiovascular system is described as two pumps (right and left ventricles) connected in series and separated from each other by the pulmonary and systemic circulation. Output of the right ventricle (RV) provides the input (venous return) for the left ventricle (LV) through the pulmonary circulation with a lag time of two beats [1].

Cardiopulmonary interactions can be substantially understood on the basis of the effects of changes in intrathoracic pressure (ITP) and lung volume on the determinants of cardiovascular performance: atrial preload, ventricular afterload, myocardial contractility, and heart rate. Changes in ITP are transmitted to the intrathoracic structures: the heart and pericardium, the great arteries and veins [2]. These interactions are observable in health and can be increased or modified in the presence of diseases or mechanical ventilation (MV).

The effects of spontaneous ventilation on the circulation were first documented in 1733 by Stephen Hales, showing that the blood pressure of healthy people fell during spontaneous inspiration. Over a century later, Kussmaul described the *pulsus paradoxus* (inspiratory absence of the radial pulse) in patients with tuberculous pericarditis [3].

2.1.1 Basic Physiological Concepts in Cardiopulmonary Interactions

A brief definition of some basic physiological concepts involved in cardiopulmonary interactions is essential before illustrating their effects during noninvasive ventilation (NIV).

- *Pulmonary compliance* defines the change in lung volume due to changes in transpulmonary pressure applied to the lung ($\Delta V/\Delta P$). It is a measure of the ability of the lungs to be stretched and expanded. The transpulmonary pressure is determined by the difference between pleural pressure (P_{pl}) or ITP and alveolar pressure (P_A). P_{pl} is normally a subatmospheric pressure (-5 cmH₂O) and P_A (force of airflow into and out of the lungs) is <0 cmH₂O in inspiration and >0 in expiration. The compliance is highest at moderate lung volumes, near functional residual capacity (FRC), with a normal value of 200 ml/cmH₂O, and much lower at very low volumes (toward residual volume) or very high volumes (toward total lung capacity). However, if the lung is more rigid (as in restrictive diseases), pulmonary compliance decreases, moving the pressure-volume curve to the right, whereas increases in conditions with less rigidity (emphysema) move the pressure-volume curve to the left. This concept is important when NIV is applied. Lung and chest wall compliance constitutes the total compliance of the system. In the supine position, the pressure-volume curve of the lung does not change compared with the orthostatic position, but the curve of the chest wall moves to the right because it is more difficult to stretch the chest [4].
- *Transmural pressure* (P_{tm}), also called distending pressure, is the difference between the pressure within a chamber or vessel (intramural stress or P_{in}) and the pressure around it (extramural stress or P_{ex}). The $P_{tm}(=P_{in}-P_{ex})$ describes the complex effects of changes in ITP or blood volume on the cardiac chambers. Respiration induces phasic fluctuations in cardiac P_{tm} , and inspiratory P_{pl} is lowered by the respiratory muscles during spontaneous breathing and is increased during the application of positive pressure ventilation (PPV). The resultant variation of P_{pl} determines a change in P_{ex} in the heart with a direct influence on LV and RV volume and function. The rise in P_{tm} , consequent to a fall in P_{pl} , promotes ventricular filling and impedes ejection [4].
- *Ventricular interdependence* (VI) is the influence of the RV on the LV. Anatomically, the LV and RV share a common pericardial sac, with limited volume and compliance, and a common interventricular septum [4]. The filling of one ventricle can directly influence the function of the other: an increase in RV volume during spontaneous inspiration leads to a reduction in LV compliance and, hence, LV filling. VI is considered the major cause of *pulsus paradoxus* in patients with a restrictive pericardium as a result of tamponade. This effect becomes greater as P_{pl} becomes more negative or with a fluid bolus that acutely fills the RV. The application of positive end-expiratory pressure (PEEP) can be beneficial in these conditions [4].
- *Cardiac output* (CO) is the volume of blood pumped by the LV or RV in 1 min. An average resting CO is 5.6 l/min for a male and 4.9 l/min for a female [5]. Respiration with its ITP variations influences diastolic heart filling and, hence, CO. During NIV, these respiratory changes are particularly important. CO is measured at a defined phase of the respiratory cycle, usually at end-expiration [5].
- *Ventilation/perfusion ratio* (V/Q) is not uniform in all the zones of the lung. V/Q inequalities in the lung were proposed by Permutt in 1962 and 2 years later by

West et al. [6]. In the erect position, the perfusion increases from the top to the bottom of the lung. This is a result of hydrostatic forces combined with the different effect of airway pressure. In theory, the lung is divided into three vertical regions, based on the relationship between the pressure in the alveoli (P_A), in the arteries (P_a), and the veins (P_v). *Zone 1* ($P_A > P_a > P_v$) is a region at the top of the lung in which P_a falls below P_A . It is not observed in the normal healthy human lung, because P_a exceeds P_A in all parts of the lung. This is generally observed in marked hypotension or during NIV. In these circumstances, capillaries remain collapsed and low perfusion occurs (dead space). In zone 1, V/Q is the highest. *Zone 2* ($P_a > P_A > P_v$) is the part of the lung about 3 cm above the heart, where pulmonary P_a is greater than P_A , but P_v remains below P_A . In this region, blood flows in pulses. *Zone 3* ($P_a > P_v > P_A$) includes the majority of the lung in health. In this zone, both P_a and P_v exceed P_A , producing continuous blood flow throughout the cardiac cycle.

- *Pulmonary vascular resistance (PVR)* is the flow resistance that must be overcome to push blood through the vasculature of the lungs. The total resistance of the pulmonary circulation depends on the balance in the vascular tone of its two components: the *alveolar vessels* and the *extra-alveolar* or *parenchymal vessels*. PVR is closely related to lung volume, rising at both extremes of lung volume variations (Fig. 2.1). PVR is minimal at FRC. When the lungs are inflated above FRC toward total lung capacity (TLC), alveolar vessels become compressed as a result of alveolar distension or hyperinflation. As lung volume falls from FRC toward residual volume, extra-alveolar vessels become progressively more tortuous and tend to collapse and terminal airway collapse at low volumes causing

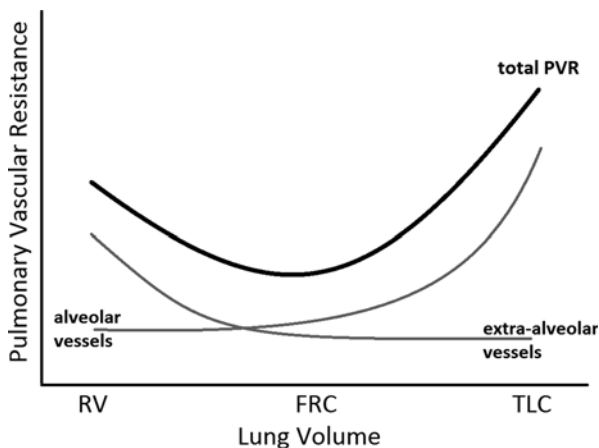


Fig. 2.1 Schematic representation of the relation between lung volumes and pulmonary vascular resistance (*PVR*). Alveolar and extra-alveolar resistance determine the *PVR*. As lung volume increase from residual volume (*RV*) to total lung capacity (*TLC*), the alveolar vessels become compressed by distending alveoli and their resistance increases, whereas the extra-alveolar vessels become less tortuous with a fall of their resistance. At functional residual capacity (*FRC*) *PVR* is lowest

alveolar hypoxia. *Hypoxic pulmonary vasoconstriction* independently increases PVR. In addition, lower pH leads to increased pulmonary vasoconstriction.

Hereafter, these concepts will be applied to the interactions in cardiopulmonary function in spontaneous breathing, during NIV, and in the presence of respiratory and cardiac diseases.

2.1.2 Cardiopulmonary Interaction During Spontaneous Breathing

In spontaneous breathing, the contractions of the diaphragm and intercostal muscles reduce ITP, leading to a greater pressure gradient according to the values of atmospheric and airway pressure. The decrease in ITP is transmitted to the intrathoracic organs, resulting in a fall in cardiac P_{ex} and a rise in P_{tm} . The increase in P_{tm} promotes RV diastolic filling. Consequently, RV increases stroke volume via the Frank-Starling mechanism [5]. The subsequent rise in pulmonary flow increases LV pressure load and its end-diastolic volume. Also, LV P_{ex} falls and P_{tm} rises during inspiration, increasing LV afterload during the systole. As a result, LV stroke volume and systolic blood pressure fall and LV end-systolic volume rises [5]. Thus, the main consequences of the decrease in ITP during spontaneous breathing are an increase in LV afterload and an increase in RV preload (Table 2.1).

In healthy subjects, spontaneous inspiration is usually associated with a slight fall in systolic blood pressure (<10 mmHg). During spontaneous inspiration, both P_{pl} and intravascular aortic pressure fall, but the fall in P_{pl} is relatively greater than the fall in aortic pressure, increasing P_{tm} and resulting in an increased LV afterload and a reduction in LV stroke volume.

Table 2.1 Different effects on lung and heart function

Spontaneous breathing	Noninvasive ventilation
↓ ITP (<i>negative</i>)	↑↑ ITP (<i>positive</i>)
↓ Blood systemic pressure inspiration	↓↓ Blood systemic pressure inspiration
÷ PVR	↑ PVR
↑ P_{tm}	↓ P_{tm}
↑ Venous return RA	↓↓ Venous return RA
↑ RA preload	↓ RA preload
↑ RV afterload	↑ RV afterload
↑ RV cardiac output	↓ RV cardiac output
↑ LV afterload	↓ LV afterload
↓ LV cardiac output	↑ LV cardiac output
	↑ Myocardial O ₂ consumption RV
	↓ Myocardial O ₂ consumption LV

ITP intrathoracic pressure, PVR pulmonary vascular resistance, P_{tm} transmural pressure, RA right atrium, RV right ventricle, LV left ventricle

Increased respiratory efforts with a greater variation of P_{pl} and P_{tm} , as in asthma and pulmonary edema, or increased sensitivity to changes in P_{tm} in the heart, as in hypovolemia and congestive cardiac failure, leads to a decrease in systolic blood pressure during inspiration more than 10 mmHg, creating pulsus paradoxus [3].

The effect of spontaneous breathing on pulmonary blood vessels is generally irrelevant and hardly ever causes a significant drop in systolic pressure. In addition, changes in lung volumes during spontaneous ventilation rarely determine an increase in PVR.

Neurohumoral processes probably play a primary role in the long-term effects of ventilation on the cardiovascular system. However, most of the immediate effects of ventilation on the heart are secondary to changes in autonomic tone. The lungs are richly enervated with somatic and autonomic fibers that mediate different homeostatic processes and instantaneously alter the cardiovascular function. The most common of these are the vagally mediated heart rate changes during ventilation [7]. Inflation of the lung to normal tidal volumes (<10 ml/kg) induces vagal-tone withdrawal, accelerating heart rate. This phenomenon is known as respiratory sinus arrhythmia and can be used to document normal autonomic control, especially in patients with diabetes who are at risk for peripheral neuropathy [7]. Inflation to larger tidal volumes (>15 ml/kg) decreases heart rate by a combination of both increased vagal tone and sympathetic withdrawal. Sympathetic withdrawal also determines arterial vasodilation. This inflation/vasodilation response can reduce LV contractility in healthy subjects and, as reported below, in ventilator-dependent patients with the initiation of high-frequency ventilation or hyperinflation [7].

2.2 Interactions on Cardiopulmonary Function in NIV

Mechanical ventilation, applying a positive pressure on inspiration and increasing ITP, produces physiological effects that are directly opposite from normal spontaneous ventilation. The positive ITP is transmitted to the alveoli and the interstitial tissues. Intrapulmonary and interstitial pressures remain positive in inspiration and return toward atmospheric pressure on expiration. If a PEEP is added, ITP remains positive even in expiration. As in spontaneous breathing, MV is associated with an inspiratory fall in aortic flow and systolic blood pressure, but the mechanism is considerably different [8].

In the 1940, Cournand et al. [9] studied the physiological effects of a PPV on cardiac function, demonstrating a variable reduction in CO in healthy subjects receiving PPV. Cournand showed that RV filling was inversely related to ITP, and as this became more positive the RV preload fell, producing an evident fall in CO.

PPV determines a simultaneous rise in ITP and in lung volumes. The increase in lung volume plays a significant role in the hemodynamic changes during NIV: tidal volumes are often higher than those in spontaneous breathing.

The interactions with cardiopulmonary function during NIV are complex and may depend on baseline cardiopulmonary function and, in a certain way, differences in the mode of ventilation.

The main hemodynamic effects of PPV include a decrease in venous return of RV and LV, an increase in VI, an increase in PVR, an increase in central venous pressure, and a decrease in LV afterload (Table 2.1).

The positive ITP decreases venous return and alters RV and LV ejection. Increased lung volume enlarges RV size by raising PVR, causing intraventricular cardiac septum shift and decreasing LV filling. In addition, augmented ITP reduces LV afterload, increasing ejection of blood from LV. These effects are proportional to the amount of positive pressure, inspiratory volume, and value of PEEP [4].

The decrease in preload and blood pressure essentially depends on the volume status of the patient and is more pronounced in conditions of reduced venous return (hypovolemia and vasodilation). This is primarily due to the influence of ITP on venous return of RV, leading to a fall in left heart output. Considering ventilation modalities, the decrease in preload and blood pressure can be greater with controlled modes of MV with high tidal volume and high airway pressure. Thus, the application of assisted MV modalities (CPAP, BiPAP, PSV), maintaining a spontaneous inspiratory effort, is favored in these cases [10].

Conversely, patients with fluid overload and congestive heart failure considerably benefit from PEEP or PPV and may radically improve after its application. Because ITP is higher during NIV, volume infusion stabilizes the relationship between venous return and CO.

The intrathoracic cardiovascular system is often described as two sections (RV and LV) connected in series. Therefore, it is clinically more practical to consider the effects of NIV on right and left heart (Table 2.1).

- *Effects of NIV on right heart:* the effects on right heart are mainly characterized by a decrease in venous return (RA preload), an increase of RV afterload, and a decrease in RV coronary flow. PVR is the main determinant of RV afterload and is directly affected by changes in lung volume (Fig. 2.1). PVR rises during NIV, determining increased work for the right heart and decreased filling for the left heart.

The decrease of venous return, especially in patients with hypovolemia (real or relative), determines a complex compensatory sympathetic response with tachycardia, vasoconstriction, oliguria, and retention of water and NaCl [4]. Increased RV afterload, especially when using high tidal volumes, results in an increase of RV work and O₂ consumption. For this reason, the use of low tidal volumes is preferable in patients with acute cor pulmonale.

- *Effects of NIV on left heart:* the effects on the left heart include a decrease in LA preload, the reduction of LV afterload, an increase in stroke volume, decrease in O₂ consumption, and increase of CO. The reduction of LV afterload is the most relevant effect during NIV, restoring the hemodynamics to a more favorable position on the Starling curve: P_{tm} (distending pressure) decreases with a high ITP ($P_{tm} = P_{in} - ITP$). Therefore, patients with left heart failure show a functional improvement during NIV, even if limited by the decrease in venous return for high levels of PEEP.

Extrinsic PEEP ($PEEP_e$), increasing mean P_A and also P_{pl} , is commonly used to recruit alveoli, defend end-expiratory lung volume, and improve oxygenation during MV. Some data support the neurohumoral-mediated effects of PEEP on cardiac function in addition to its mechanical effects [10]. The achievement of the best value of PEEP is based on the balance between the respiratory benefits of PEEP and its adverse cardiovascular and respiratory effects.

Physiologically, V/Q inequalities coexist in the different zones of the lung. Alveolar recruitment is essential for the efficacy of NIV. The state of the airways, their resistance, and the alveolar compliance determine the effect of the pressure in different regions of the lung. These factors define the individual *time constant* of the different regions. Positive pressure preferentially aerates high compliance areas at the expense of lower compliance areas, whereas collapsed alveoli may require higher constant pressure to be opened. The variation in time constants between alveoli and lung regions precludes a single pressure as suitable for all lung regions [11].

Dyspnea is the imbalance between breathing effort and chest displacement. The patient's strategy to maintain alveolar ventilation that minimizes the work of breathing (WOB) is the breathing pattern balancing the elastic and resistive ventilation forces. Increased inspiratory effort produces a large negative P_{pl} that increases LV afterload and may lead to respiratory muscle fatigue and respiratory acidosis. A positive inspiratory pressure-assist favors the reduction of patient's WOB, inspiratory effort, and dyspnea [11].

NIV does not directly depress cardiac contractility. The presence of PEEP promotes the release of cardiodepressive humoral factors. Furthermore, the alteration between O_2 demand and supply for increased RV afterload can justify a reduction in contractility, rather than the LV, where the decrease in preload and afterload reduces wall stress and O_2 demand.

In summary, conditions that can accentuate the hemodynamic effects of MV include hypovolemia and venodilation (decrease in venous return), use of large tidal volume or high $PEEP_e$ (increase in mean ITP), and anesthesia and sedatives (reduction of compensatory sympathetic reflexes). The use of volume expansion to restore LV preload, assisted modes of ventilation to reduce P_{pl} , and the avoidance of high ITP occurring with a high minute volume, high inspiratory flow, or $PEEP_e$ are efficient strategies to minimize these effects.

2.2.1 NIV and Clinical Implications in Respiratory and Cardiovascular Diseases

In patients with cardiovascular or pulmonary diseases, the application of NIV requires special consideration.

- *Cardiac diseases* are frequent in patients requiring MV. These have important hemodynamic effects during NIV depending on the type and severity of the disease. As described above, the main physiological determinants of CO are preload,

contractility, afterload, and heart rate. Changes in CO are the result of the increase in ITP, which causes a decrease in preload and afterload [11].

In cases of hypovolemia, restrictive cardiomyopathy, tamponade, or valvular stenosis, where CO is *dependent on venous return*, PPV can cause a further reduction in CO. In coronary heart disease, heart diseases with fibrosis, or hypertrophy, characterized by *reduced ventricular compliance*, increased ITP during NIV reduces LV afterload and increases CO.

In ischemic diastolic LV dysfunction with pulmonary edema, characterized by the *increase in preload and afterload*, increased intrathoracic blood volume, a positive ITP, or simply the use of PEEP can improve CO by limiting venous return and lowering LV afterload. In addition, PEEP helps to maintain alveolar patency and lung volume in these patients at risk of secondary atelectasis as a result of edema. In cases of coronary artery disease and *impaired LV contractility*, the heart is not able to compensate for the increased O₂ need and increased effort for breathing, which can increase up to 20 times and can sometimes result in cardiorespiratory arrest [2]. In LV failure, an increase in preload and afterload also increases O₂ demand of the myocardium, leading to a negative myocardial O₂ balance. The application of MV may have a favorable effect on preload and afterload reduction of LV, and reduces the need for O₂ with the correction of hypoxia and metabolic acidosis. PEEP determines improvements in oxygenation and in lung volume toward FRC and can also have a beneficial effect on RV afterload.

The effect of PPV on the RV is not so favorable. The increase in ITP and PEEP increases PVR and impairs RV function by reducing preload and increasing afterload. In subjects with pulmonary hypertension (PH), acute pulmonary embolism, COPD, or RV infarction, characterized by *afterload-induced RV dysfunction*, MV may affect the balance of RV supply and demand of oxygen. The treatment of reversible pulmonary vasoconstriction by hypoxia or acidosis and the defense of coronary perfusion pressure with pressor agents can be beneficial [8].

In heart failure secondary to RA stretch, circulating levels of natriuretic peptides increase. These hormones promote sodium and water diuresis. PPV and persistent hyperinflation decrease RA stretch mimicking hypovolemia. During PPV, plasma norepinephrine and rennin increase, whereas atrial natriuretic peptide decreases [4].

- *Pulmonary diseases* determine pathological changes in lung mechanics affecting lung volume and elasticity, airflow resistance, WOB, and RV impedance [10].

Conditions altering lung volume, with a *reduction in lung compliance and volume*, are the result of bronchial obstruction (inflammation, secretions), an increase in lung elastance (pulmonary edema, pneumonia, acute respiratory distress syndrome (ARDS)), a reduction in FRC (anesthesia, supine posture, abdominal and thoracic trauma), or an increase in closing volume.

Any variation in lung volume increases PVR (Fig. 2.1) and increases RV load.

A reduction in lung volume increases the resistance in extra-alveolar pulmonary vessels due to hypoxic vasoconstriction, structural distortion, and

vasoconstrictor mediators (thromboxanes). This condition also increases the dependence and interaction of LV function on the RV.

The prevention of acute right heart failure due to excessive increase in PVR can be achieved by avoiding NIV with large volumes and high pressure. Alveolar recruitment and reversal of hypoxia and acidosis are important efforts to reduce PVR. After the initiation of MV in patients with severe lung diseases, assisted ventilation modes are recommended utilizing fluid therapy to improve LV preload and inotropic agents to support CO.

Pulmonary diseases with *increased airway resistance* (asthma, COPD) prolong the expiratory time and oppose alveolar deflation resulting in dynamic hyperinflation and creating intrinsic PEEP ($PEEP_i$). $PEEP_i$ is the lowest P_A that must be overcome by the inspiratory muscles to initiate inspiratory gas flow. As already mentioned, increased lung volume reduces venous return of RV and LV. Dynamic hyperinflation and inspiratory airflow limitation both increase the inspiratory effort to maintain alveolar ventilation. Consequently, the increased ITP at expiration increases LV afterload and reduces venous return, producing a greater fall in systolic blood pressure and increasing the possibility of paradoxical pulse. Extreme expiratory effort with increase in WOB can cause respiratory arrest and sudden death in severe bronchospasm [2]. Hence, MV may further increase dynamic hyperinflation and P_{pl} in presence of severe airflow limitation. Ventilatory settings must carefully avoid further air trapping, using a long expiratory time and avoiding large tidal volume, high frequency, and prolonged inspiratory time. In these patients, assisted modes of ventilation, reducing the threshold work and inspiratory effort and improving minute volume, minimize the hemodynamic effects of MV. Although $PEEP_e$ reduces WOB, it is recommended to avoid $PEEP_e$ in excess of $PEEP_i$ [11].

Most pulmonary diseases are associated with an increase in minute volume and an *increase in respiratory effort per breath (WOB)*. High minute volume demand may result from an elevation in metabolic rate or deterioration in gas exchange. The metabolic cost of breathing, normally only 1–2 % of total body O_2 consumption, may rise to as much as 20 % in acute respiratory failure. MV has therapeutically beneficial effects on WOB by reducing O_2 consumption and preserving cardiac function. Significant negative deflections in both esophageal and transdiaphragmatic pressure characterize chronic lung diseases with elevated spontaneous WOB. Applying a PEEP, NIV reduces WOB by counterbalancing $PEEP_i$, reducing the threshold load to inspiration, and by increasing respiratory-system compliance, reducing the elastic load to inspiration. In general, an inspiratory pressure-support level of 15 cmH_2O and a PEEP of 5 cmH_2O reduce most measures of WOB and inspiratory effort toward normal [11].

In pulmonary diseases with *increased RV impedance* (afterload), *increase in lung volume* progressively increases alveolar vessel resistance. Hyperinflation can cause considerable hemodynamic compromise and create significant PH and precipitate acute cor pulmonale and RV ischemia. PH is a frequent complication of pulmonary embolism, acute exacerbation of chronic lung disease, ARDS, and chronic pulmonary disease. PH increases RV afterload and induces acute RV

dilatation and progressive RV failure. This may significantly reduce pulmonary flow and LV preload and precipitate systemic hypotension. The combination of systemic hypotension and PH has an unfavorable effect on RV myocardial O₂ supply and demand. In addition, most inotropic agents have pulmonary vasoconstrictor properties. In these cases, noradrenaline appears to have the best profile by producing less pulmonary vasoconstriction for comparable levels of inotropic effect and support of myocardial perfusion [4]. Appropriate ventilatory management in PH aims at avoiding factors that exacerbate pulmonary vasoconstriction: hypoxia, hypercapnia or acidosis, atelectasis, and excessive changes in lung volume. MV reduces pulmonary vasomotor tone by counteracting hypoxic pulmonary vasoconstriction, increasing O₂ alveolar partial pressure, PEEP recruitment of collapsed alveoli, and small lung volume toward FRC, and reducing respiratory acidosis and central sympathetic output, which decreases the stress of breathing.

ARDS is characterized by markedly increased lung elastance, alveolar collapse, airflow limitation, pulmonary hypertension, and elevated metabolic rate and WOB. Humoral inflammatory mediators can produce pulmonary vasoconstriction, myocardial depression, and systemic hypotension. During MV in ARDS, a greater inspiratory airway pressure is required to maintain adequate alveolar ventilation, and high levels of PEEP are often utilized to prevent airway collapse and aid recruitment of alveoli. Moreover, RV dysfunction during MV is due to the combined effects of positive ITP and presence of elevated PVR. In ARDS, maintenance of RV preload (volume loading), RV contractility (inotropic agents), and systemic blood pressure (pressor agents) with clinical and hemodynamic assessment is essential. The requirement for an ideal MV mode in ARDS, without adverse respiratory and cardiac side effects, has led to the proposal of the use of high-frequency ventilation, inverse ratio ventilation, extracorporeal oxygenation, inhaled pulmonary vasodilators, and prone ventilation [4].

Finally, the evaluation of *fluid status* during the initiation of PPV is crucial. An acute reduction in systemic venous return is one of the most commonly observed cardiopulmonary interactions. The inflation-vasodilatation response due to vagal overstimulation can further aggravate it. This can be particularly dramatic in hypovolemic patients and in vasodilated patients with systemic sepsis. The respiratory variation in arterial pressure induced by MV, initially described as reversed pulsus paradoxus, is currently considered a predictor of fluid responsiveness and not an indicator of blood volume [10].

Conclusions

Respiration and circulation are complementary physiological processes that interact with each other during spontaneous breathing. The introduction of MV and the presence of pulmonary and cardiac diseases increase the complexity of this interaction. ITP decreases during spontaneous inspiration and increases during PPV. Thus, the different hemodynamic responses during spontaneous and positive-pressure breathing are related to the changes in ITP and the energy