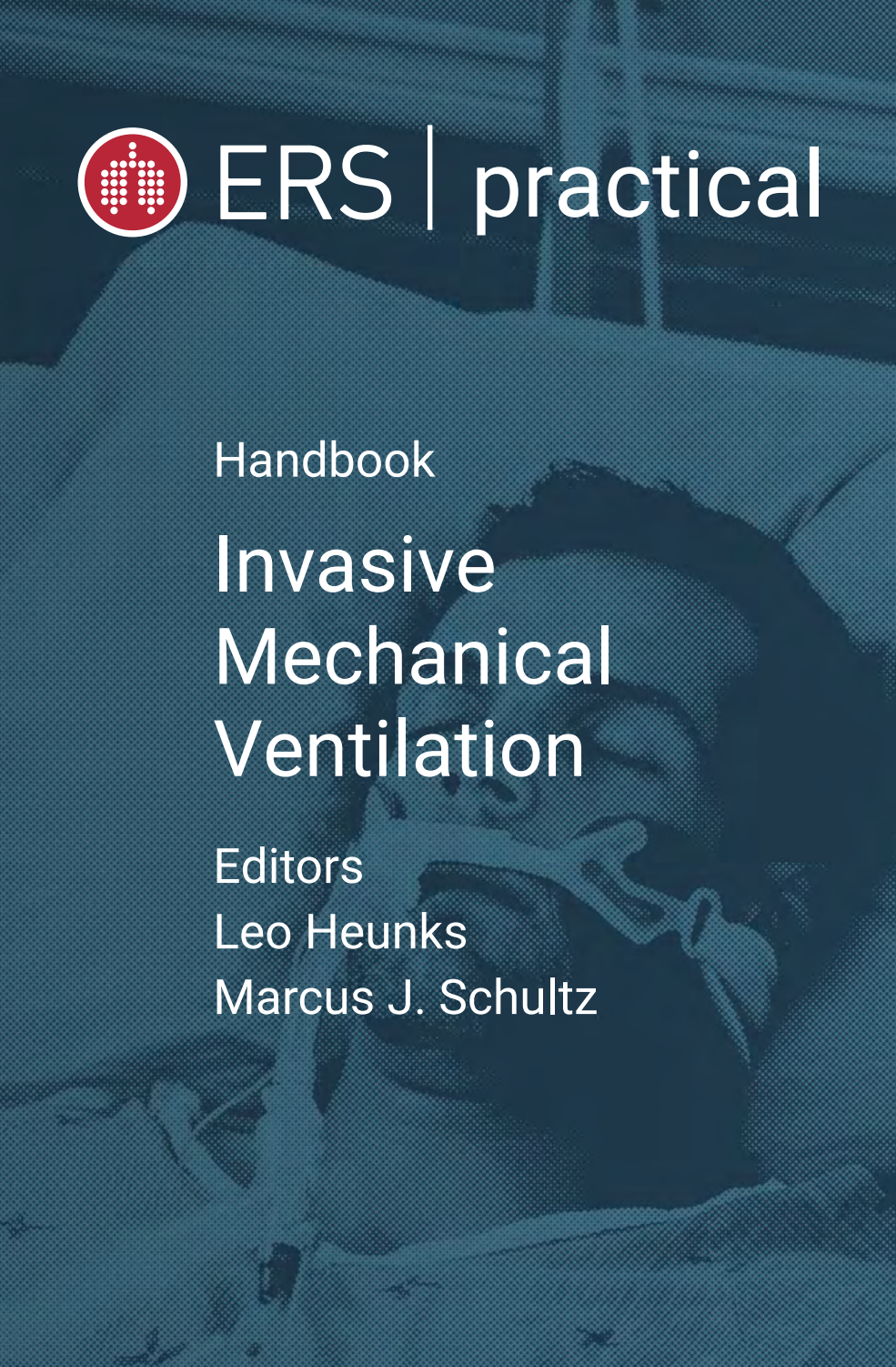

ERS | practical

Handbook

# Invasive Mechanical Ventilation

Editors
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# Preface

"读万卷书不如行万里路"
"First read plenty of books, then travel plenty of places"
*Confucius, 551–479 BC*

Thank you for picking up this *ERS Practical Handbook of Invasive Mechanical Ventilation*. In doing so you are probably interested in artificial ventilation in general, and "invasive ventilation" in particular, but you also appear interested in reading a medical book. The former is not surprising if you are a doctor or nurse treating patients in need of ventilatory support: artificial ventilation is the cornerstone of the treatment of acute respiratory failure. The interesting question is, why would you still read a medical book in 2020? Many people have unrestricted access to hundreds of medical journals online, in addition to a variety of apps, podcasts and online videos. All these "electronic" services provide an endless amount of useful, if not practical information, and such media undoubtedly will become even more important now artificial intelligence and machine learning have entered our profession. New sources of information are a fantastic achievement, which have not only increased, and continue to increase access to information, but have probably also improved patient care, and thus patient outcomes.

However, with so much information at hand one may not see the wood for the trees. Indeed, during our daily rounds or when teaching trainees, we noticed that trainees were very aware of the most recently published RCTs on ventilatory support but frequently lacked a basic knowledge of ventilator modes, patient–ventilator interaction and ways to monitor invasively ventilated patients.

For instance, we are all aware of the RCTs that have shown survival benefit when using a low *versus* a high $V_T$ in patients with ARDS. But does it matter whether a low $V_T$ is delivered in a controlled mode, in a partially supported mode, or maybe in an automated, artificial intelligence-driven mode? Is a low $V_T$ always protective? Does a low $V_T$, maybe, affect patient–ventilator interactions, respiratory muscle function, or even haemodynamics? To answer these questions, a fundamental understanding of the basics of invasive ventilation is required.

But there are several other topics to be discussed at the bedside. How should we act when hypoxaemia becomes refractory? When should we consider prone positioning and how does prone positioning improve outcome? What are the effects on ventilation/perfusion ratios? Is there still a role for inhalation

therapies, lung recruitment manoeuvres and extracorporeal oxygenation and decarboxylation? What are their indications, and how are they best applied in clinical practice? What are the principles of artificial ventilation in patients with obstructive lung diseases or patients with interstitial lung diseases? This handbook provides concise information that is useful at the bedside for safe ventilation in patients with different lung diseases, written by recognised experts.

A prerequisite for safe invasive ventilation is adequate respiratory monitoring. Clinicians have several techniques available at the bedside, including pulse oximetry, chest radiography and CT, and lung ultrasound, but also more sophisticated techniques, such as electrical impedance tomography and oesophageal pressure measurements. Experts in this field describe the principles of these techniques, possible indications and pitfalls. This will help the clinician to choose the appropriate monitoring technique for invasively ventilated patients under different clinical conditions.

Last but not least, the process of liberating a patient from invasive ventilation, *i.e.* weaning, requires much attention. How can partially supported modes or automated modes help here? And what if a patient fails to wean? When can a tracheostomy be helpful? Especially in awake, spontaneously breathing patients, it could be important to monitor patient–ventilator interactions, respiratory mechanics and breathing efforts. Although many scientific papers have been published about weaning from invasive ventilation, very few provide clinical guidance about how to set the ventilator in a weaning patient. Experts in the field of ventilator weaning provide useful recommendations about how to ventilate patients during the weaning process and a practical approach to the difficult to wean patient.

All the of above is covered in the chapters in this book that all follow a similar approach: providing basic background information, helpful graphics, a summary of the evidence, and finally a list for further reading.

To finish, we would like to express our sincere gratitude to the authors that have contributed to this book – they are the experts and the knowledge-base that drives this book. Selection of authors for this book was by an invitation to the members of Assembly 2 of the European Respiratory Society (ERS), made during the ERS International Congress in Paris, France in 2018. Both early career members and senior members responded enthusiastically and spent their valuable time writing these chapters for you. We would also like to thank the ERS publications office for their support and hard work to complete this ambitious project. And thank you, dear reader, for picking up this handbook. We hope you enjoy reading it and that it helps you to improve your understanding of the basics of invasive ventilation. After reading this book, you will spend more time at the bedside applying what you learned from the

nicely written chapters in this book. Choosing the correct individual settings, the best mode, closely observing how the ventilator and patient interact, and understanding what you actually monitor will certainly further improve your knowledge of invasive mechanical ventilation. To paraphrase Confucius: First read plenty of books, than observe and manage plenty of ventilated patients.

**Leo Heunks and Marcus J. Schultz**
***Chief Editors***

# Get more from this Handbook

By buying the *ERS Practical Handbook of Invasive Mechanical Ventilation*, you also gain access to the electronic version of the book, as well as an accredited online CME test.

Simply visit http://ersbookshop.com/titles and add the *ERS Practical Handbook of Invasive Mechanical Ventilation* to your cart. At the checkout, enter the unique voucher code printed on the inside front cover of the book. You will then be able to download the entire book in PDF format to read on your computer or mobile device.

You'll also be able to take the online CME test. This Practical Handbook has been accredited by the European Board for Accreditation in Pneumology (EBAP) for 8 CME credits.

**Also available from the ERS**

**ERS Practical Handbook of Noninvasive Ventilation**
*Edited by Anita K. Simonds*

This handbook provides a concise 'why and how to' guide to NIV from the basics of equipment and patient selection to discharge planning and community care.
Leading clinicians and researchers in the field have been brought together to provide an easy-to-read guide to all aspects of NIV. Topics covered include: equipment, patient selection, adult and paediatric indications, airway clearance and physiotherapy, acute NIV monitoring, NIV in the ICU, long-term NIV, indications for tracheostomy ventilation, symptom palliation, discharge planning and community care, and setting up an NIV service.

# List of abbreviations

| | |
|---|---|
| **AHI** | Apnoea–hypopnoea index |
| **AIDS** | Acquired immunodeficiency syndrome |
| **ALS** | Amyotrophic lateral sclerosis |
| **ARDS** | Acute respiratory distress syndrome |
| **ARF** | Acute respiratory failure |
| **ASB** | Assisted spontaneous breathing |
| **ASV** | Adaptive servo ventilation |
| **ASSPCV** | Assisted pressure-controlled ventilation |
| **AVAPS** | Average volume-assured pressure support |
| **BMI** | Body mass index |
| **CF** | Cystic fibrosis |
| **COPD** | Chronic obstructive pulmonary disease |
| **CPAP** | Continuous positive airway pressure |
| **ECG** | Electrocardiogram |
| **EPAP** | Expiratory positive airway pressure |
| **$FEV_1$** | Forced expiratory volume in 1 s |
| **$F_{IO_2}$** | Inspiratory oxygen fraction |
| **FVC** | Forced vital capacity |
| **HIV** | Human immunodeficiency virus |
| **ICU** | Intensive care unit |
| **IPAP** | Inspiratory positive airway pressure |
| **IPPV** | Intermittent positive pressure ventilation |
| **IVAPS** | Intelligent volume-assured pressure support |
| **NIV** | Noninvasive ventilation |
| **NPV** | Negative pressure ventilation |
| **OHS** | Obesity hypoventilation syndrome |
| **OSA(S)** | Obstructive sleep apnoea (syndrome) |
| **$P_{aCO_2}$** | Arterial carbon dioxide tension |
| **$P_{aO_2}$** | Arterial oxygen tension |
| **PAV** | Proportional assist ventilation |
| **PCV** | Pressure-controlled ventilation |
| **PEEP** | Positive end-expiratory pressure |
| **PSV** | Pressure support ventilation |
| **$P_{tcCO_2}$** | Transcutaneous carbon dioxide tension |
| **$S_{aO_2}$** | Arterial oxygen saturation |
| **RCT** | Randomised controlled trial |
| **$S_{pO_2}$** | Arterial oxygen saturation measured by pulse oximetry |
| **TB** | Tuberculosis |
| **TLC** | Total lung capacity |
| **VCV** | Volume-controlled ventilation |
| **$V_T$** | Tidal volume |

# Conflicts of interest

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# Mechanisms of hypoxaemia and hypercapnia

Rebecca F. D'Cruz and Nicholas Hart

The primary function of the respiratory system is maintenance of gas exchange, which is achieved through ventilation, diffusion and perfusion. These processes enable oxygenation of systemic tissue and removal of carbon dioxide, a metabolic by-product of cellular respiration. An understanding of the physiological principles that cause hypoxaemia and hypercapnia underpins effective oxygenation and ventilation strategies for patients in respiratory failure.

## Hypoxaemia

Oxygen diffuses down a pressure gradient from the alveoli into the pulmonary capillaries and is transported in blood predominantly by binding reversibly to haemoglobin. Oxygenation can be quantified by measuring oxygen saturation, which represents the proportion of haemoglobin binding sites bound to oxygen, and $P_{aO_2}$, which quantifies the amount of oxygen dissolved in plasma. $S_{aO_2}$ reflects the oxygen content of arterial blood, $S_{pO_2}$ reflects oxygen content measured by pulse oximetry. Although it is difficult to define a normal range for $P_{aO_2}$ given the limited data in healthy subjects, ranges of 90–110 mmHg (12.0–14.6 kPa) can be applied, with a value of <60 mmHg (8.0 kPa) diagnostic of hypoxaemia. Hypoxaemia should be distinguished from hypoxia, which is insufficient oxygen at the cellular level, categorised as:

- hypoxic (low $P_{aO_2}$ and $S_{aO_2}$),
- anaemic (reduced oxygen-carrying capacity of blood),

### Key points

- Hypoxaemia and hypercapnia are quantified with arterial partial pressures of oxygen ($P_{aO_2}$) and carbon dioxide ($P_{aCO_2}$).
- Abnormal gas exchange may be evaluated by calculating the alveolar–arterial $P_{O_2}$ gradient ($P_{O_{2(A-a)}}$) and the $P_{aO_2}$ (mmHg) to fraction of inspired oxygen ($F_{IO_2}$) ratio ($P_{aO_2}/F_{IO_2}$).
- The five principal causes of hypoxaemia are ventilation/perfusion mismatch, hypoventilation, diffusion limitation, right-to-left shunt and reduced inspired oxygen tension.
- Hypercapnia arises as a consequence of imbalance in the load–capacity–drive relationship of the respiratory muscle pump.

- circulatory (insufficient oxygen delivery), or
- histotoxic (cells cannot utilise oxygen despite normal delivery).

$P_{O_2(A-a)}$ can be used to determine the presence of abnormal gas exchange:

$$P_{O_2(A-a)} = P_{AO_2} - P_{aO_2}$$

where $P_{AO_2}$ is the alveolar oxygen tension.

Using the alveolar gas equation:

$$P_{AO_2} = P_{IO_2} - P_{aCO_2}/R$$

where $P_{IO_2}$ is the partial pressure of inspired oxygen and R is the respiratory exchange ratio (taken as 0.8).

Defining the alveolar–arterial gradient requires accurate quantification of $P_{IO_2}$. This can be achieved during invasive ventilation, but is unreliable when supplementary oxygen is delivered *via* nasal cannula or a standard facemask. Calculation of $P_{aO_2}$ (mmHg) to fraction of inspired oxygen ($F_{IO_2}$) ratio ($P_{aO_2}/F_{IO_2}$) is more practical and may be used to define and monitor patients with ARDS. A $P_{aO_2}/F_{IO_2}$ of ≤300 mmHg (40.0 kPa) indicates impaired gas exchange.

### Hypercapnia

Carbon dioxide is transported in the blood predominantly as bicarbonate and is quantified using $P_{aCO_2}$ (normal reference range 34–45 mmHg (4.6–6.0 kPa)). $P_{aCO_2}$ is the gold standard to diagnose hypercapnia and should be measured prior to commencing or discontinuing invasive ventilation. In a steady clinical state with normal cardiac output, central or mixed venous samples correlate closely with $P_{aCO_2}$; however, peripheral venous $P_{CO_2}$ correlates poorly and should not be used as a surrogate measure of $P_{aCO_2}$.

Arterial blood gases performed to obtain $P_{aCO_2}$ are invasive and painful; therefore, alternative methods of carbon dioxide monitoring may be implemented. $P_{tcCO_2}$ measures carbon dioxide diffusing through the skin using a heated skin probe that causes local arterialisation. Earlobe placement of a probe heated to 42ºC produces $P_{tcCO_2}$ values that correlate acceptably with $P_{aCO_2}$. If available, $P_{tcCO_2}$ can be used to continuously monitor carbon dioxide trends to support monitoring of clinical progress and response to interventions.

Capnography can be used during invasive ventilation to measure carbon dioxide at the airway opening and involves an infrared absorption sensor positioned in the ventilator circuit. The capnography waveform comprises four phases:

- Phase I measures inspired gas and early expiration of anatomical dead space, where carbon dioxide is absent
- Phase II measures expired alveolar gas, therefore $P_{CO_2}$ rises steeply
- Phase III measures the plateau of expired alveolar gas, providing a value for end-tidal $P_{CO_2}$ ($P_{ETCO_2}$)
- Phase IV commences at inspiration of the next breath at which carbon dioxide falls back to zero

When ventilation and perfusion are perfectly matched, $P_{ETCO_2}$ accurately reflects alveolar and therefore arterial carbon dioxide. However, if alveolar ventilation and perfusion are mismatched, $P_{ETCO_2}$ underestimates $P_{aCO_2}$. Expiratory time set on the ventilator may also cause $P_{ETCO_2}$ to underestimate $P_{aCO_2}$ by cutting expiration short before a representative end-tidal value is obtained. Absolute values of $P_{ETCO_2}$ should therefore not be used as a surrogate of $P_{aCO_2}$ to monitor clinical trajectory in critical care or during decision making for weaning from invasive ventilation. However, $P_{ETCO_2}$ trends may be useful to monitor patients' progress and may be used by advanced ventilator modes which can adjust settings based on $P_{ETCO_2}$. $P_{ETCO_2}$ is also valuable in confirmation of endotracheal tube placement and indication of return of spontaneous circulation following cardiac arrest.

## Respiratory failure

Hypoxaemic type 1 respiratory failure ($P_{aO_2}$ <60 mmHg (8.0 kPa)) represents intrinsic lung failure. Hypercapnic type 2 respiratory failure ($P_{aCO_2}$ >45 mmHg (6.0 kPa)) represents failure of the respiratory muscle pump, in which there is imbalance in the load–capacity–drive relationship of the respiratory system. Causes of hypoxaemia are listed in table 1.

## Mechanisms of hypoxaemia

*Ventilation/perfusion mismatch* $P_{aO_2}$ is determined by the ratio of alveolar ventilation to pulmonary perfusion. Lung areas with a higher $V'/Q'$ ratio (high ventilation relative to perfusion) have higher $P_{AO_2}$ and lower alveolar carbon dioxide tension ($P_{ACO_2}$) and contribute minimally to arterial oxygenation. Areas with a lower $V'/Q'$ ratio (low ventilation relative to perfusion) have lower $P_{AO_2}$ and higher $P_{ACO_2}$ and contribute more to gas exchange since they are better perfused. Pathological processes that increase heterogeneity of lung ventilation and perfusion increase $V'/Q'$ mismatch, with the net effect of hypoxaemia.

$V'/Q'$ mismatch may also lead to hypercapnia. This may be mitigated by compensatory hyperventilation triggered by chemoreceptors that increase neural respiratory drive (NRD) in response to rising hydrogen ions as a consequence of increased $P_{aCO_2}$. Due to the linear shape of the carbon dioxide dissociation curve, increased minute ventilation tends to normalise hypercapnia through increased carbon dioxide elimination from regions of both high and low $V'/Q'$ ratios. Hypoxaemia may be improved but cannot be corrected by hyperventilation due to the sigmoid shape of the oxygen dissociation curve, which benefits only lung regions with a moderately low $V'/Q'$ ratio. In obstructive lung disease, which is characterised by expiratory flow limitation, increased respiratory rate shortens the time available for adequate expiration. The consequent acute increase in end-expiratory lung volume is termed dynamic hyperinflation, which increases work of breathing, due to the elastic and threshold loads it imposes, and may impair ventilation and lead to hypercapnia, due to increased physiological dead space. Other compensatory mechanisms to mitigate the effects of hypoxaemia include increased oxygen uptake by peripheral tissue and increased cardiac output.

$V'/Q'$ mismatch is the commonest cause of hypoxaemia and can be quantified using $P_{O_{2(A-a)}}$, with an increased gradient reflecting greater mismatch.

*Table 1. Mechanisms of hypoxaemia*

| Mechanism | Causes |
|---|---|
| **Ventilation/perfusion ($\dot{V}'/\dot{Q}'$) mismatch** | Low $\dot{V}'/\dot{Q}'$<br>COPD<br>Asthma<br>Pulmonary oedema<br>Interstitial lung disease |
| | High $\dot{V}'/\dot{Q}'$<br>Pulmonary embolism |
| **Hypoventilation** | NRD depression<br>Pharmacological<br>Cortical/brainstem ischaemia, haemorrhage or trauma |
| | Nerve/neuromuscular junction pathology<br>Spinal cord lesion<br>Poliomyelitis<br>Motor neuron disease<br>Guillain–Barré syndrome<br>Myaesthenia gravis |
| | Muscle weakness<br>Muscular dystrophy<br>Inflammatory myopathy<br>Critical illness<br>Hyperinflation (functional respiratory muscle weakness)<br>Electrolyte imbalance<br>Thyroid myopathy |
| | Chest wall abnormality<br>Obesity<br>Kyphoscoliosis<br>Flail chest |
| **Diffusion limitation** | Interstitial lung disease |
| **Shunt** | Anatomical<br>Intracardiac<br>Pulmonary arteriovenous malformation<br>Hepatopulmonary syndrome |
| | Physiological<br>ARDS<br>Pneumonia<br>Atelectasis |
| **Reduced $P_{IO_2}$** | Altitude |

*Hypoventilation* $P_{AO_2}$ is determined by alveolar ventilation and capillary uptake of oxygen. If alveolar ventilation falls, alveolar oxygen falls and carbon dioxide rises. Provided alveolar perfusion remains stable, the diffusion gradient between the alveoli and pulmonary capillaries consequently falls, giving rise to hypoxaemia and hypercapnia.

*Diffusion limitation* Thickening of the blood–gas barrier causes incomplete gas transfer *via* diffusion between the alveoli and pulmonary capillaries. Diffusion

limitation alone is insufficient to cause resting hypoxaemia, but hypoxaemia may manifest during exercise (when increased cardiac output reduces erythrocyte time in the pulmonary circulation, which reduces the time available for adequate gas exchange) or in combination with *V′/Q′* mismatch, which may occur in interstitial lung diseases.

*Shunt* Right-to-left shunting is when blood passes from the right to left side of the heart without passing through ventilated lung. This profound *V′/Q′* mismatch causes hypoxaemia that cannot be corrected with 100% inspired oxygen. The degree of response in $P_{aO_2}$ to 100% inspired oxygen depends on the shunt fraction:

$$Q_S/Q_T = (C_{cO_2} - C_{aO_2})/(C_{cO_2} - C_{vO_2})$$

where $Q_S$ is pulmonary physiologic shunt, $Q_T$ is cardiac output, $C_{cO_2}$ is pulmonary capillary oxygen content, $C_{aO_2}$ is arterial oxygen content and $C_{vO_2}$ is mixed venous oxygen content.

*Reduced inspired oxygen tension* $P_{IO_2}$ falls with barometric pressure, which occurs at altitude. Referring to the alveolar gas equation, $P_{aO_2}$ theoretically falls at the same rate as $P_{IO_2}$, provided $P_{CO_2}$ and R remain constant. In practice, hypoxia at altitude stimulates hyperventilation, which lowers carbon dioxide and increases $P_{O_2}$ compared with at sea level.

## Mechanisms of hypercapnia

Hypercapnia is a consequence of imbalance in the loads, capacity and drive of the respiratory muscle pump (figure 1).

*Respiratory muscle load* Loads imposed on the respiratory muscle pump may be resistive (secondary to airways obstruction, bronchospasm or secretions) or elastic as a consequence of reduced respiratory system compliance (as in obesity, scoliosis, chest wall disease, hyperinflation, pleural effusion and abdominal distension, which reduce extrinsic chest wall compliance; or pneumonia, alveolar oedema, atelectasis and interstitial lung disease, which reduce intrinsic lung compliance). If present, intrinsic positive airways pressure ($PEEP_i$) imposes a threshold load which must be overcome to generate inspiratory flow. $PEEP_i$ is characteristic of obstructive lung disease, in which increased airways resistance limits expiratory airflow, resulting in hyperinflation. $PEEP_i$ may also occur in obesity where breathing at low $V_T$ causes early airway closure.

Respiratory muscle loads can be quantified by measuring the transdiaphragmatic pressures required to generate airflow using gastric and oesophageal balloon catheters connected to a pressure transducer. The area under the diaphragm pressure curve defines the pressure–time product, which reflects respiratory muscle load. $PEEP_i$ is measured as the change in oesophageal pressure generated prior to the onset of inspiratory flow.

*Inspiratory muscle capacity* Inspiratory muscle capacity may be impaired where there is pathology of the spinal cord, peripheral nerves, neuromuscular junction or skeletal muscle (table 1), and can be quantified with maximal voluntary inspiratory manoeuvres, including sniff nasal pressure and maximum inspiratory pressure at

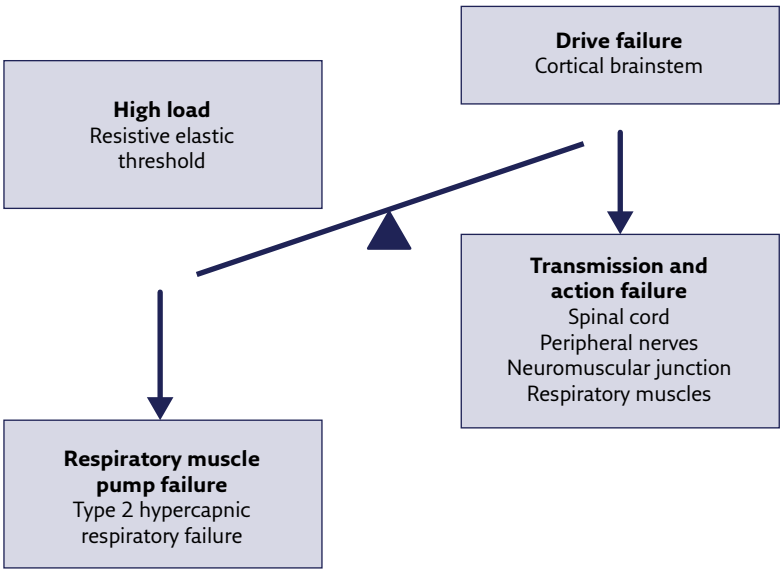


*Figure 1. Type 2 hypercapnic respiratory failure is an imbalance between NRD, the load on the respiratory muscles and capacity of the respiratory muscles. Reproduced from Suh* et al. *(2012),* Medicine; *40: 293–297, with permission.*

the mouth. For patients who cannot perform maximal voluntary manoeuvres, such as patients in intensive care, twitch transdiaphragmatic pressure with phrenic nerve magnetic stimulation can be performed in specialist centres.

*Neural respiratory drive* NRD reflects the balance between respiratory muscle load and capacity. As it is not possible to directly measure output from the central respiratory control centre, surrogate measures are applied in clinical practice. Mouth occlusion pressure in the first 100 ms of inspiration at functional residual capacity ($P_{0.1}$), measured with a pneumotachograph and one-way valve, is a simple and noninvasive marker of NRD. $P_{0.1}$ in healthy subjects is ~1 $cmH_2O$. Large differences between $P_{0.1}$ and minute ventilation indicate increased respiratory muscle load. $P_{0.1}$ is less reliable at higher operating lung volumes and with airflow resistance, particularly in patients with obstructive lung disease and $PEEP_i$. Electromyography of the diaphragm ($EMG_{di}$, using a gastro-oesophageal multipair electrode catheter) or parasternal muscles ($EMG_{para}$, using surface electrodes) has been used as a physiological biomarker reflecting NRD. $EMG_{para}$ has been used to monitor inpatient clinical trajectory during severe COPD exacerbations and can predict COPD patients who are safe to be discharged from hospital. $EMG_{para}$ also reflects disease severity and exercise-induced breathlessness in COPD, asthma and cystic fibrosis.

## Summary

Hypoxaemia ($P_{aO_2}$ <60 mmHg (8.0 kPa)) is most commonly caused by $\dot{V}/\dot{Q}$ mismatch. Hypercapnia ($P_{aCO_2}$ >45 mmHg (6.0 kPa)) is a consequence of

imbalance in the loads and capacity of the respiratory muscle pump, which can be assessed by measuring NRD. The alveolar–arterial $P_{O_2}$ gradient ($P_{O_2(A-a)}$) and $P_{aO_2}/F_{IO_2}$ ratio are used to evaluate gas exchange abnormalities. Management of respiratory failure must always involve identification and treatment of the underlying pathophysiology.

## Further reading


- D'Cruz RF, *et al.* (2018). Positive airway pressure devices for the management of breathlessness. *Curr Opin Support Palliat Care*; 12: 246–252.
- Jolley CJ, *et al.* (2009). A physiological model of patient-reported breathlessness during daily activities in COPD. *Eur Respir Rev*; 18: 66–79.
- Wagner PD (2015). The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. *Eur Respir J*; 45: 227–243.
- West J (2015). West's Respiratory Physiology: The Essentials. Philadelphia, Lippincott Williams and Wilkins.

# Respiratory mechanics

Guilherme Benfatti Olivato, Robert Huhle, Marcelo Gama de Abreu and Ary Serpa Neto

Invasive ventilation with positive pressure promotes relevant changes in respiratory system mechanics, and there are several variables with clinical relevance that can be measured during invasive ventilation. Currently, most ventilators display ventilatory curves, for example airway pressure, gas flow and respiratory system volume. Using modelling, data on respiratory mechanics can be derived from these signals.

Monitoring of the respiratory system mechanics should be conducted routinely on every patient submitted to invasive ventilation. Among several possibilities, its applications include:

1) diagnosis;
2) correct titration of ventilatory settings according to physiological thresholds and therapeutic goals; and
3) continuous assessment of the response to the treatment.

This chapter highlights the concepts of basic monitoring of respiratory mechanics in patients under invasive ventilation.

## Resistance

Gas flow originates from a pressure gradient, from the higher pressure towards the lower. In patients undergoing invasive ventilation, this may exist between

**Key points**

- Monitoring of respiratory system mechanics should be conducted routinely on every patient submitted to invasive ventilation.
- Resistance of the airway ($R_{aw}$) is the relationship between the pressure gradient in the airways and flow ($P_{aw} - P_{plat}$/flow).
- $C_{rs}$ is the relationship between the inspiratory volume and the variation of pressure inside the chest wall and the lungs ($V_T/P_{plat}$ – PEEP).
- The mechanical power of ventilation, which can be calculated from routinely measured ventilator parameters, has been associated with pulmonary inflammation, oedema and in-hospital mortality in critical ill patients.

the trachea ($P_{tr}$) and the alveoli ($P_{alv}$). Therefore, when the tracheal and alveolar pressures are known, for an established flow, it is possible to calculate the airway resistance. The relationship between the pressure gradient in the airways and flow determine the resistance of the airway ($R_{aw}$). Assuming the flow during inspiration is constant, the following formula can be considered:

$$R_{aw} = \frac{P_{tr} - P_{alv}}{\text{Flow}} \quad (1)$$

For patients under invasive ventilation, the pressure is measured before the endotracheal tube; therefore, the resistance measured using proximal inspiratory pressure, mentioned as the pressure in the airway ($P_{aw}$), is in fact the sum of the resistances of the endotracheal tube and of the patient's airway, being referred to as the total $R_{aw}$ of the respiratory system. This difference between the $P_{aw}$ and the $P_{alv}$ is called resistive pressure ($P_{res}$), and as $P_{alv}$ equals the airway pressure during zero flow end-inspiration occlusion $P_{plat}$, the $R_{aw}$ can therefore be summarised as (figure 1):

$$R_{aw} = R_{aw}(\text{tube}) + R_{aw}(\text{patient}) = \frac{P_{aw} - P_{alv}}{\text{Flow}} = \frac{P_{res}}{\text{Flow}} = \frac{P_{aw} - P_{plat}}{\text{Flow}} \quad (2)$$

The unit of measurement of $R_{aw}$ is $cmH_2O{\cdot}s{\cdot}L^{-1}$ and values considered normal in humans are between 4 and 8 $cmH_2O{\cdot}s{\cdot}L^{-1}$, depending on the internal diameter of

$$R_{aw} = \frac{P_{peak} - P_{plat}}{\text{Flow}} = \frac{40 - 30}{1} = 10\ cmH_2O{\cdot}s{\cdot}L^{-1}$$

$$C_{rs} = \frac{V_T}{P_{plat} - \text{PEEP}} = \frac{500}{30 - 5} = 20\ mL{\cdot}cmH_2O^{-1}$$

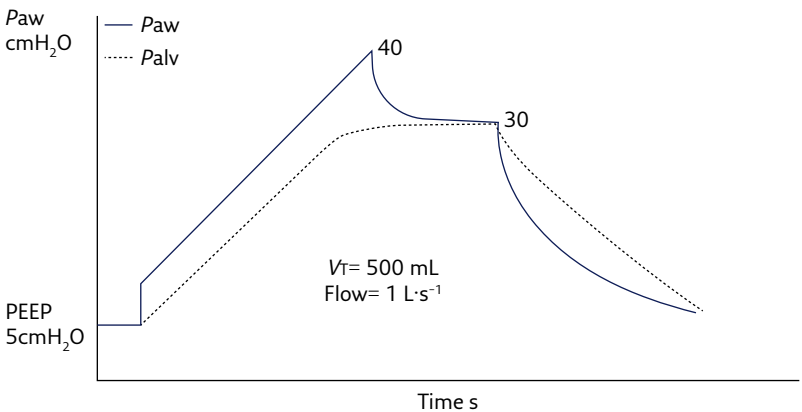


*Figure 1. Calculation of* $R_{aw}$ *and* $C_{rs}$ *of the respiratory system in a patient under volume-controlled invasive ventilation. Knowing the* $V_T$*, with constant or rectangular inspiratory flow and measuring the* $P_{plat}$ *and* $P_{peak}$*,* $R_{aw}$ *and* $C_{rs}$ *can be calculated. Reproduced and modified from Barbas* et al. *(2014),* Rev Bras Ter Intensiva; *26: 89–121, with permission.*

*Table 1. Expected ranges of the variables discussed*

| | $R_{aw}$ $cmH_2O \cdot s \cdot L^{-1}$ | $C_{rs}$ $mL \cdot cmH_2O^{-1}$ | Mechanical power $J \cdot min^{-1}$ |
|---|---|---|---|
| **Normal** | 4–8 | 60–80 | Not defined |
| **ARDS** | 4–8 | 35–45 | Not defined |
| **COPD** | 10–30 | 50–70 | Not defined |

the tube and the presence or absence of an obstruction to the air flow in the airway (table 1). Conditions such as bronchospasm and the presence of secretions in the airway are the most common causes of elevation in $R_{aw}$.

## Compliance

The increase in pulmonary volume during the inspiratory phase leads to pulmonary and chest wall expansion, stretching the elastic structures of the respiratory system. Similar to a spring system, the elastic structure exerts opposite forces proportional to the deformation, which is in turn equivalent to the inspiratory volume. This elastic force, diffused through the lung's surface, generates positive intrapulmonary pressure. The relationship between the inspiratory volume ($\Delta V$) and the variation of pressure inside the chest wall and the lungs ($\Delta P$) corresponds to the respiratory system compliance ($C_{rs}$):

$$C_{rs} = \frac{\Delta V}{\Delta P} \quad (3)$$

In the presence of PEEP, the difference in pressure due to the inspiratory volume, is the difference between the $P_{alv}$ and the PEEP. The $C_{rs}$ can therefore be summarised as:

$$C_{rs} = \frac{\Delta V}{P_{alv} - PEEP} \quad (4)$$

Compliance is the variable that evaluates the stiffness of the respiratory system. During ventilatory support, $C_{rs}$ represents the relationship between the $\Delta V$ and the difference between $P_{plat}$ and the pressure at the end of expiration (PEEP):

$$C_{rs} = \frac{\Delta V}{P_{plat} - PEEP} \quad (5)$$

The unit of measurement of $C_{rs}$ is $mL \cdot cmH_2O^{-1}$ and values considered normal are around 60–80 $mL \cdot cmH_2O^{-1}$ (table 1). Its inverse is called elastance (defined as $1/C_{rs}$). $C_{rs}$ may be reduced in clinical scenarios like tuberculosis, pulmonary fibrosis or ARDS.

While $C_{rs}$ as described above can be determined during tidal ventilation without any additional intervention, the quasi-static compliance of the respiratory system ($C_{stat}$)

is measured during prolonged end-inspiratory occlusion and during slow inflation manoeuvres. In contrast to the commonly used $C_{rs}$, the true $C_{stat}$ is the compliance of the respiratory system with any viscoelastic stress and strain at equilibrium with zero flow. However, to date, the additional clinical value of measuring $C_{stat}$ compared with $C_{rs}$ has not been shown and thus it is rarely measured in clinical practice.

### Resistance and compliance in clinical practice

The measurement of the $P_{plat}$ is mandatory for the calculation of respiratory mechanics. To identify the resistive and elastic elements throughout the respiratory cycle, the inspiratory pause, that delays the opening of the expiratory valve is of unique importance. During an inspiratory pause there is no flow in the airway, therefore, the pressure measured at the end of this pause ($P_{plat}$) is close to the $P_{alv}$. In addition, the pressure measured immediately before the pause is the $P_{peak}$. Yet, in every respiratory cycle the ventilator measures the variation in volume, namely the $V_T$ and the flow (figure 1). Thus, in clinical practice, $R_{aw}$ and $C_{rs}$ are calculated according to equations (2) and (5), defined above.

Respiratory mechanics modelled by resistance and compliance require a passive respiratory system, *e.g.* without spontaneous breathing activity. Recent results of modelling only portions of the expiratory signals suggest that an approximation is possible in assisted ventilation modes. However, care must be taken that no spontaneous breathing activity is overlapping with the analysed signal portion.

### Lung compliance and transpulmonary pressure

The respiratory system has two main tissue components: the lung parenchyma, that fills the cavity formed by the chest wall, and the diaphragm. The parenchyma consists of a soft tissue containing different amounts of elastin and collagen fibres. The lung parenchyma has a higher mechanical compliance compared with the chest wall, which is formed by solid bones, and the diaphragm, the major muscle driving spontaneous breathing. The compliance of the parenchyma is subject to huge variations due to pathology and therapy during invasive ventilation (*e.g.* oedema, collapse). The compliance of the chest wall and the diaphragm may be considered as time invariant during short to medium intervals of invasive ventilation, but might be subject to externally restricted movement.

The transpulmonary pressure ($P_L$) can be derived as the difference between $P_{alv}$ and the pressure in the pleura ($P_{pl}$), a liquid filled double membrane that connects the lung to the chest wall without restricting lung movement along the latter:

$$P_L = P_{alv} - P_{pl} \tag{6}$$

Lung compliance ($C_L$) can be obtained by:

$$C_L = \frac{V_T}{P_{plat} - PEEP - (P_{plat,L} - PEEP_L)} \tag{7}$$

where $P_{plat,L}$ is transpulmonary end-inspiratory pressure and $PEEP_L$ is transpulmonary end-expiratory pressure. $P_{pl}$ is subject to hydrostatic alterations, depending on the body position. In the supine position, ventral pleural pressure can be up to 10 $cmH_2O$ lower than dorsal pleural pressure. Similarly, in caudal regions

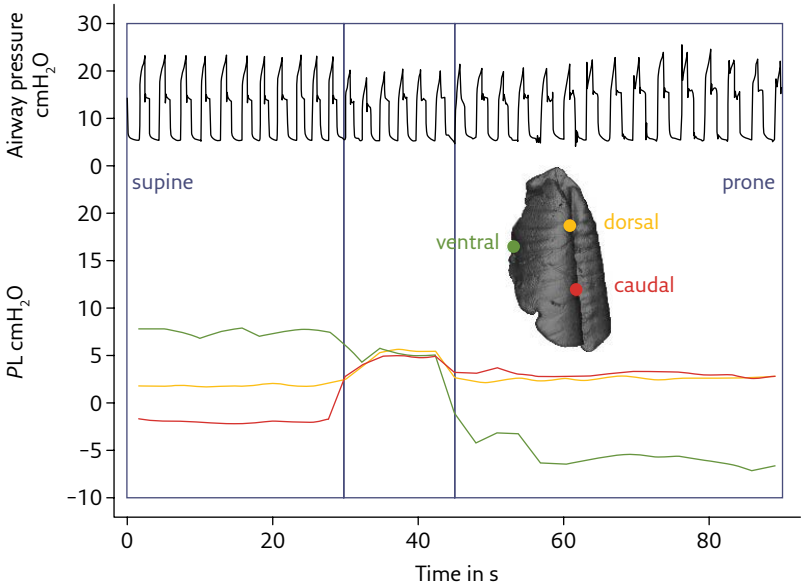


*Figure 2. Transpulmonary pressure (*P*L) in ventral (green), dorsal (yellow) and caudal (red) regions in a healthy pig during shifting from a supine to prone position during volume-controlled ventilation.*

the weight of the abdominal cavity increases $P_{pl}$. If $P_{pl}$ exceeds $P_{alv}$, the $P_L$ becomes negative. This essentially means that the respective alveoli collapse as the alveolus' exterior pressure exceeds its internal pressure. Therefore, dorsal and caudal lung regions are more prone to collapse in the supine position (figure 2).

As the direct local measurement of $P_{pl}$ is highly invasive, it is not suitable for clinical application. However, a minimally invasive surrogate for the average $P_{pl}$ of the whole lung is assessable through measurement of oesophageal pressure ($P_{oes}$). This is increasingly used in clinical scenarios, such as PEEP titration, assessing the amount of spontaneous breathing, and potentially muscular work and power of ventilation.

### Mechanical work and mechanical power

To overcome resistive and elastic forces during tidal controlled invasive ventilation as well as during spontaneous breathing, mechanical work (MW) or mechanical energy is performed by the ventilator and/or by the respiratory muscles, respectively. The derivation of MW and mechanical power (MP) from the routinely measured respiratory signals during controlled invasive ventilation and an approximation from the respiratory mechanical parameters resistance and compliance is presented in this section.

Mechanical energy or MW during tidal ventilation is derived by integration of $P_{aw}$ change over the respective change of $V_T$:

$$MW = \int_{(V_T)} \Delta P_{aw}(V)dV \quad (8)$$

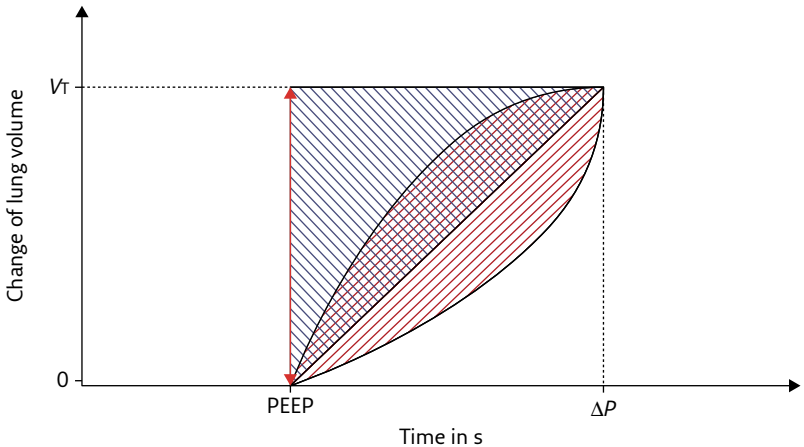


*Figure 3. Change of lung volume during tidal ventilation with PEEP, driving pressure (ΔP) and tidal volume ($V_T$). Elastic MW (blue lines), resistive MW during inspiration (red lines) and during expiration (crossed) areas are shown; airway pressure does not change from zero to PEEP during tidal ventilation and thus no PEEP-related MW is present (area is zero, indicated by the red double arrow).*

Conversely, inspiratory MW can be calculated integrating the inspiratory pressure volume curve from zero to $V_T$. This MW is spent to overcome the elastic and resistive components of the respiratory system.

The expiratory MW is derived when integrating the expiratory pressure volume curve from $V_T$ to zero (figure 3). While inspiratory MW is positive, expiratory MW is negative from the perspective of the ventilator, as this work is performed by the elastic recoil forces of the respiratory system. One part of this expiratory MW is spent pushing volume back into the expiratory branch of the ventilator circuit and another part is used to overcome resistive forces during expiration. As both the resistive and the elastic components of the respiratory system govern the MW, the later can be expressed as a function of dynamic respiratory system compliance ($C_{dyn}$) and respiratory system resistance ($R_{aw}$):

$$MW = \int_{(V_T)} \left( R_{aw} \cdot \dot{V} + \frac{1}{C_{dyn}} \cdot V \right) dV \quad (9)$$

Assuming constant flow, volume-controlled invasive ventilation with a rectangular inspiratory flow curve and constant resistance and compliance during inspiration:

$$MW = \left( R_{aw} \cdot \frac{1+I:E}{60 \cdot I:E} \cdot RR + \frac{1}{2 \cdot C_{dyn}} \right) \cdot V_T^2 \quad (10)$$

where I:E is inspiratory to expiratory ratio and RR is the respiratory rate.

MP may be derived from MW by multiplication with RR:

$$MP = RR \cdot V_T^2 \cdot \left( \frac{1}{2} EL_{rs} + RR \cdot \frac{(1+I:E)}{60 \cdot I:E} \cdot R_{aw} \right) \quad (11)$$

where $EL_{rs}$ is the elastance of the respiratory system.

A minimisation of MP is discussed as a bedside tool to avoid development of VILI (table 1). MP was associated with neutrophilic inflammation in a retrospective analysis of a study in an experimental model of ARDS. MP was furthermore associated with in-hospital mortality in critical ill patients in a retrospective study.

During spontaneous breathing, all the mechanical work involved is performed by the respiratory muscles. Hence, equation (8) becomes:

$$MW = \int_{(V_T)} P_{mus}(V) dV \quad (12)$$

with intra-thoracic pressure generated by the respiratory muscles ($P_{mus}$) to achieve a respective $V_T$; however, the measurement of oesophageal and static recoil pressure of the chest wall is necessary. In assisted invasive ventilation a comparable method may be used with good agreement with equation (8).

## Summary

Mechanical ventilators can continuously measure airway flow, pressure and volumes, allowing the calculation of $R_{aw}$ and $C_{rs}$, and the display of volume–pressure and flow–volume loops. Whereas routine measurement of local $P_{pl}$ is not feasible in clinical practice, measurement of its minimally invasive surrogate $P_{oes}$ has gained increased attention and might be useful in clinical practice. However, its potential to improve clinical outcome remains uncertain. The mechanical work and power of ventilation, which can be calculated from routinely measured ventilator parameters, have been associated with pulmonary inflammation, oedema and in-hospital mortality in critical ill patients. However, further research is warranted to define their potential as targets for invasive ventilation.

## Further reading


- Gattinoni L, *et al.* (2016). Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med*; 42: 1567–1575.
- Huhle R, *et al.* (2019). Power of ventilation and its relationship with neutrophilic inflammation in a double hit model of acute respiratory distress syndrome. *Am J Respir Crit Care Med*; 199: A7250.
- Kiss T, *et al.* (2019). Effects of positive end-expiratory pressure and spontaneous breathing activity on regional lung inflammation in experimental acute respiratory distress syndrome. *Crit Care Med*; 47: e358–e365.
- Marini JJ (1990). Lung mechanics determinations at the bedside: instrumentation and clinical applications. *Respir Care*; 35: 669–696.

- Sassoon CSH, *et al.* (1998). Work of breathing during mechanical ventilation. *In:* Marini JJ, *et al.*, eds. Physiological Basis of Ventilator Support. New York, Marcel Dekker; pp. 261–302.
- Serpa Neto A, *et al.* (2018). Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. *Intensive Care Med*; 44: 1914–1922.
- Shapiro R, *et al.* (1998). Monitoring of the mechanically ventilated patient. *In:* Marini JJ, *et al.*, eds. Physiological Basis of Ventilatory Support. New York, Marcel Dekker; pp. 709–771.
- Stenqvist O (2003). Practical assessment of respiratory mechanics. *Br J Anaesth*; 91: 92–105.
- Tobin MJ (1990). Respiratory monitoring. *JAMA*; 264: 244–251.
- Yoshida T (2019). Guiding ventilation with transpulmonary pressure. *Intensive Care Med*; 45: 535–538.

# Effects of invasive ventilation on the lungs

Irene Cavalli, Tommaso Tonetti and V. Marco Ranieri

## Definition, pathophysiological and clinical features

Invasive ventilation is the supportive therapy for patients with acute respiratory failure that rests the respiratory muscle while providing adequate gas exchange. With this purpose invasive ventilation is a lifesaving technique. Extensive studies on the impact of invasive ventilation on patients with several forms of acute respiratory failure (ARDS; patients undergoing general anaesthesia; and brain death candidates subject to organ donation) have demonstrated that the inappropriate application of invasive ventilation can worsen/induce lung injury (VILI).

VILI is characterised by inflammatory cell infiltrates, hyaline membranes, increased vascular permeability and pulmonary oedema. Histologically, this damage resembles the damage that occurs in ARDS patients. However, several experimental studies have shown that injurious ventilatory regimens may alter alveolar–capillary barrier permeability inducing oedema, impair endothelial and epithelial cells, and induce an inflammatory response even in previously healthy lungs. Clinically, this damage causes impaired gas exchange and a decrease in lung and respiratory system compliance. Both increase the number of days of ventilator dependency and mortality.

VILI may occur at both high and low lung volumes. At high lung volumes, overdistention can increase alveolar–capillary permeability leading to pulmonary oedema (volutrauma). It can also cause alveolar rapture and air leak (barotrauma). By contrast, at low lung volumes the damage may be determined by the cyclic opening and closing of airways and lung units (atelectrauma), resulting in surfactant malfunction and local hypoxia. The physical forces involved in these phenomena may induce the activation of

**Key points**

- Invasive ventilation can cause VILI in previously damaged lung and even in healthy lungs.
- Improve protective invasive ventilation in any eligible patient.
- Target VILI using simple, available and repeatable tools such as $P_{plat}$ and $\Delta P$, without forgetting that other factors (such as PEEP and respiratory rate) may be equally important in determining VILI.

inflammatory mediators within the lung (biotrauma). The latter may then be released in the systemic circulation, leading to multiorgan dysfunction.

The damage caused by invasive ventilation submits the lung to non-physiological lung stress and strain. Stress represents the net force applied to the lung parenchyma, opposed by the elastic force of alveolar wall. Strain represents the deformation of a structure, defined as the change in length or volume from the initial length or volume. From a pulmonary perspective, stress is the alveolar distending pressure (alveolar pressure minus pleural pressure, *i.e.* transpulmonary pressure); and strain is the ratio of volume change (*i.e.* $V_T$) to functional residual capacity (FRC).

## Protective invasive ventilation

The concept of VILI is now generally accepted, thus the goal of invasive ventilation is to provide gas exchange while minimising VILI.

A landmark study by the ARDS network demonstrated a significant mortality reduction (31% *versus* 39.8% of the control group) when invasive ventilation was performed according to the lung-protective ventilation protocol: low $V_T$ ($V_T$ of 6 mL per kg predicted body weight (PBW)), $P_{plat}$ <30 $cmH_2O$ and moderate PEEP. This protocol also decreased the number of days of ventilator dependency when compared with traditional invasive ventilation ($V_T$ of 12 mL per kg PBW and $P_{plat}$ <50 $cmH_2O$). A flowchart of protective invasive ventilation and the setting of PEEP/$F_{IO_2}$ are available in figure 1 and in table 1, respectively.

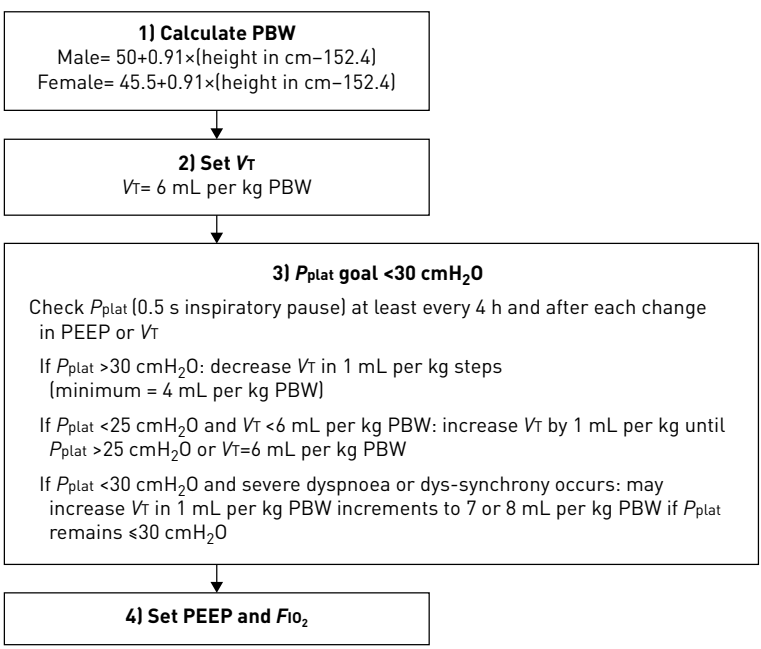


*Figure 1. Invasive ventilation protocol. Information from The Acute Respiratory Distress Syndrome Network,* et al. *(2000).*

*Table 1. Setting of PEEP/$F_{IO_2}$*

| PEEP $cmH_2O$ | $F_{IO_2}$ |
|---|---|
| 5 | 0.3–0.4 |
| 8 | 0.4–0.5 |
| 10 | 0.5–0.7 |
| 12 | 0.7 |
| 14 | 0.7–0.9 |
| 16–18 | 0.9 |
| 18–24 | 1.0 |

Information from The Acute Respiratory Distress Syndrome Network, *et al.* (2000).

While a reduction in $V_T$ has shown noticeable benefits in terms of VILI reduction, the best PEEP setting is still a challenge. In fact, setting PEEP prevents the damage that occurs at low lung volume. Nevertheless, on one hand a low PEEP may be not sufficient to keep the alveoli open; while on the other hand, a higher PEEP may have haemodynamic consequences and may be associated with lung overdistension. Several studies based on a population of ARDS patients have tried to find the best PEEP able to improve oxygenation while minimising the side-effects of inappropriate PEEP level. A meta-analysis of three large RCTs comparing higher *versus* lower PEEP in the context of lung-protective invasive ventilation showed a significant reduction in mortality in moderate and severe ARDS patients when the higher PEEP strategy was used. No significant effect was found among patients with mild ARDS, in which a strategy of high PEEP levels can even be harmful. All in all, the results of the meta-analysis suggest treating patients with moderate and severe ARDS with higher rather than lower PEEP levels. Another RCT compared lung recruitment associated with PEEP titration according to the best respiratory system compliance *versus* low PEEP levels in patients with moderate and severe ARDS. In this case the routine use of lung recruitment and titrated PEEP increased mortality compared with low PEEP. These findings suggest avoiding the routine use of lung recruitment and PEEP titration in these populations. More recently, an RCT has compared PEEP titration with an oesophageal pressure-guided strategy *versus* an empirical high PEEP–$F_{IO_2}$ strategy in a population of patients with moderate-to-severe ARDS. No significant difference in death and ventilator-free days was found comparing the two strategies. These findings do not support a PEEP titration strategy guided by oesophageal pressure instead of an empirical high PEEP–$F_{IO_2}$ strategy. Hence, the best method to set PEEP remains uncertain in ARDS patients and is even less clear in non-ARDS patients. Different methods based on lung mechanics, imaging or transpulmonary $P_{plat}$ have been proposed and require further investigation.

### Monitoring during invasive ventilation: strategies that may reduce incidence of VILI

Despite protective invasive ventilation, accurate respiratory monitoring is necessary in order to minimise the risks, preventing further injury and allowing the lungs and airways to heal. The measurement of different pulmonary mechanical variables may be useful to guide invasive ventilation and minimise VILI.

*Plateau pressure* $P_{plat}$ refers to the pressure applied to the small airways and alveoli during the end-inspiratory pause, when there is no flow and proximal airway pressure equilibrates with the alveolar pressure. An end-inspiratory occlusion manoeuvre (0.5 s) during volume-controlled ventilation (VCV) allows the measurement of $P_{plat}$. It has been demonstrated that a $P_{plat}$ value <28–30 $cmH_2O$ prevents lung overdistension. It is possible to keep the $P_{plat}$ value under the threshold of 28–30 $cmH_2O$ by reducing $V_T$.

$P_{plat}$ is the pressure at the end of an occlusion of the airways at end-inspiration. As such, $P_{plat}$ represents alveolar pressure, *i.e.* the elastic distending pressure of lungs and chest wall provided the patient is not actively contracting the respiratory muscles. Measuring $P_{plat}$ therefore allows estimation of the elastic distending pressure applied to the lung during controlled-mode invasive ventilation. Clarifications are necessary if a volume-controlled or a pressure-controlled mode of ventilation is used.

During VCV (figure 2), the peak inspiratory pressure is the sum of the elastic and resistive pressure. Thus, during an end-inspiratory occlusion manoeuvre, the flow ceases and airway pressure falls until it reaches a steady state ($P_{plat}$) allowing quantification of the elastic recoil pressure of the respiratory system.

By contrast, during pressure-controlled ventilation (PCV) (figure 3), the preset pressure limit ($P_{max}$) reflects the total pressure applied to the respiratory system in its resistive and elastic components. If the inspiratory flow does not reach zero, the preset pressure does not equal the $P_{plat}$. Hence, the $P_{max}$ during PCV does not reflect

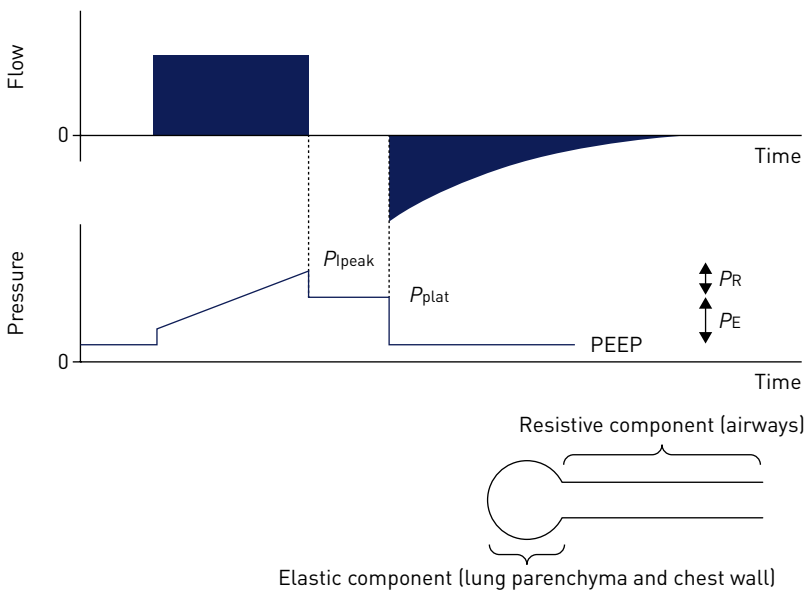


*Figure 2. Airway pressure and flow waveforms during constant flow VCV. The effect of an end-inspiratory occlusion manoeuvre is shown.* $P_{Ipeak}$*: peak inspiratory pressure;* $P_R$*: resistive pressure;* $P_E$*: elastic pressure.*

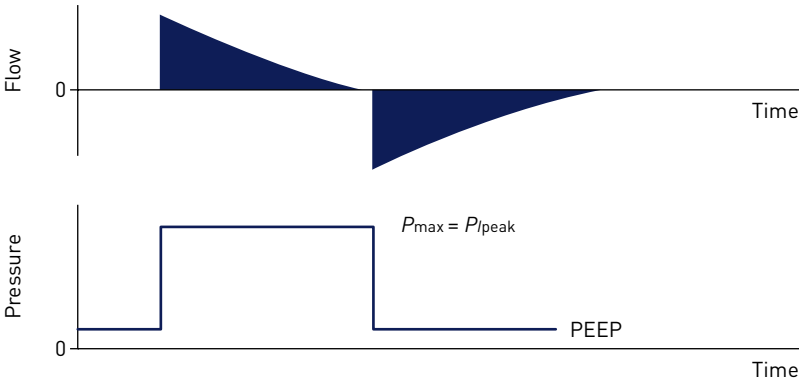


*Figure 3. Airway pressure and flow waveforms during PCV.*

the $P_{plat}$. Some mathematical corrections have been proposed in order to better estimate elastic pressure at the end of an end-inspiratory occlusion during PCV.

*Stress index* The stress index value (SI) describes the shape of the pressure–time curves during constant-flow $V_T$ delivery and muscle paralysis. During VCV, at constant flow, the rate of change in pressure is related to the changes in respiratory system compliance. This is due to the fact that the contribution from airways resistance is not influenced by changes in volume during constant flow. Relying on this assumption, the airway opening pressure ($P_{AO}$) is a function of respiratory time (t):

$$P_{AO} = a \times tb + c \quad (1)$$

where $a$ represents the value of the slope of the curve, $c$ is the pressure value at time equals zero, and $b$ is a dimensionless number that describes the shape of the pressure–time curve and represents the SI. When SI=1 the pressure–time curve is linear, and the respiratory system compliance is constant during tidal inflation. When SI<1 the shape of the pressure–time curve shows a downward concavity. This means that the respiratory system compliance increases during tidal inflation suggesting tidal recruitment of collapsed alveoli and potential recruitment when adding PEEP. Thus, it is recommended to increase PEEP. When SI>1 the shape of the pressure–time curve shows an upward concavity, representing tidal hyperinflation and a decrease in compliance. In this case, it is recommended to decrease PEEP or $V_T$ (figure 4).

Markers of injurious ventilation were minimised using ventilator settings associated with $0.9<b<1.1$.

*Transpulmonary pressure* Pressure applied on the lungs, or transpulmonary pressure ($P_L$), is the difference between airway pressure ($P_{aw}$) and pleural pressure ($P_{pl}$):

$$P_L = P_{aw} - P_{pl} \quad (2)$$

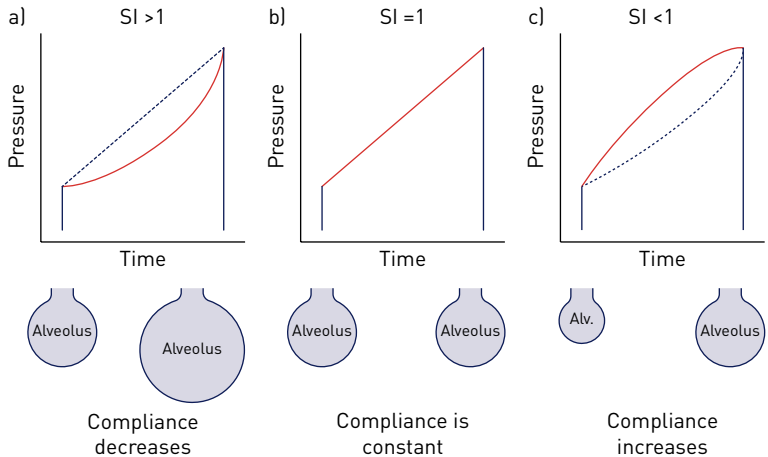


*Figure 4. a) SI with overdistension, b) normal SI, and c) SI with tidal recruitment.*

The $P_L$ reflects the distending pressure of the lung. For patients not making respiratory effort and mechanically ventilated, the $P_{aw}$ measured during a period of zero flow is called the $P_{plat}$ and represents the alveolar pressure. The $P_{plat}$ can be easily estimated at the end inspiration, when airflow is zero. Estimating $P_{pl}$ is more difficult because of the lack of noninvasive techniques. However, a minimally invasive technique is represented by oesophageal pressure ($P_{oes}$) measurement *via* a catheter with an air-filled thin-walled latex balloon inserted nasally or orally. This measurement is considered representative of $P_{pl}$. Thus, equation 2 becomes:

$$P_L = P_{plat} - P_{oes} \quad (3)$$

Other authors have shown that the absolute value of $P_{oes}$ cannot be used as surrogate measure of the $P_{pl}$ and they propose that the relative variations in $P_{oes}$ and airway pressures should be used instead to estimate $P_L$.

$P_{plat}$ is the most common variable used in clinical practice to identify lung overdistention. However, $P_{plat}$ alone can misrepresent the stress on the lung parenchyma in at least two extreme (but not very rare) cases: 1) when the chest wall is stiff; and 2) when a patient with marked dyspnoea is undergoing NIV.

1) In a patient who is not making respiratory effort (figure 5), the $P_{plat}$ represents the distending pressure of the lungs plus the chest wall. If a patient has a stiff chest wall (*e.g.* severe obesity, massive ascites, pleural effusion) much of the pressure applied by the ventilator will be used to distend the chest wall, rather than the lung. Thus, a high value of $P_{plat}$ may overestimate the real distending pressure of the lung. A stiff chest wall is associated with increases in $P_{pl}$. Thus, the measurement of the $P_{oes}$ may be useful to estimate the real $P_L$. For example, if the $P_{aw}$ is 30 $cmH_2O$ and the $P_{oes}$ is 25 $cmH_2O$, the $P_L$ will be 5 $cmH_2O$ ($P_L$=30 $cmH_2O$ – 25 $cmH_2O$=5 $cmH_2O$).

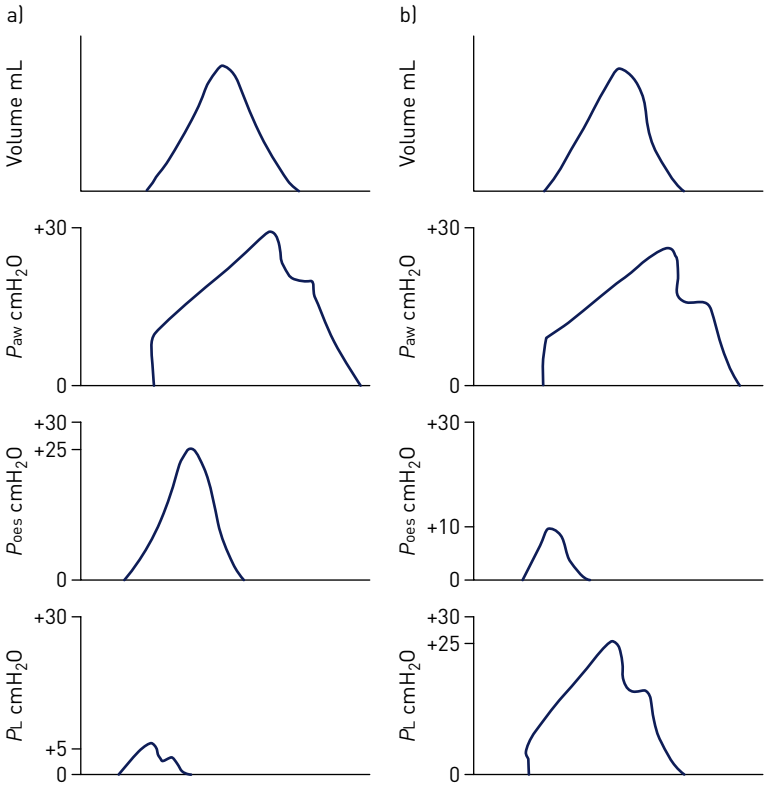


*Figure 5. Controlled invasive ventilation in a) a patient with a stiff chest wall (increased elastance of the chest wall) and b) a normal anaesthetised, paralysed patient (elastance of the chest wall is constant). In a)* $P_L = P_{aw} - P_{oes} = 30\ cmH_2O - 25\ cmH_2O = 5\ cmH_2O$, *in b)* $P_L = P_{aw} - P_{oes} = 30\ cmH_2O - 10\ cmH_2O = 20\ cmH_2O$.

2) When a patient has marked dyspnoea and spontaneous effort occurs (figure 6), large negative swings in $P_{pl}$ may occur increasing the risk of lung injury. In this case $P_{aw}$ alone may underestimate the real lung stress. For example, if $P_{aw}$ is 10 $cmH_2O$ and $P_{oes}$ is –15 $cmH_2O$, the $P_L$ will be 25 $cmH_2O$ ($P_L = 10\ cmH_2O - (-15\ cmH_2O) = 25\ cmH_2O$).

In conclusion, $P_L$ represents the distending pressure of the lung, estimated as $P_{aw}$ minus $P_{oes}$. $P_{oes}$ allows the determination of what fraction of $P_{aw}$ is applied to overcome lung and chest wall elastance.

*Driving pressure* It has been proposed that swings in pressure during invasive ventilation may be a better predictor of VILI, rather than the absolute pressure value. This swing in pressure, known as $\Delta P$, can be calculated as $P_{plat}$ minus PEEP ($\Delta P = P_{plat} - PEEP$). In a patient with ARDS, an increment in $\Delta P$ (which means a decrease in respiratory system compliance if the $V_T$ is kept constant) is associated

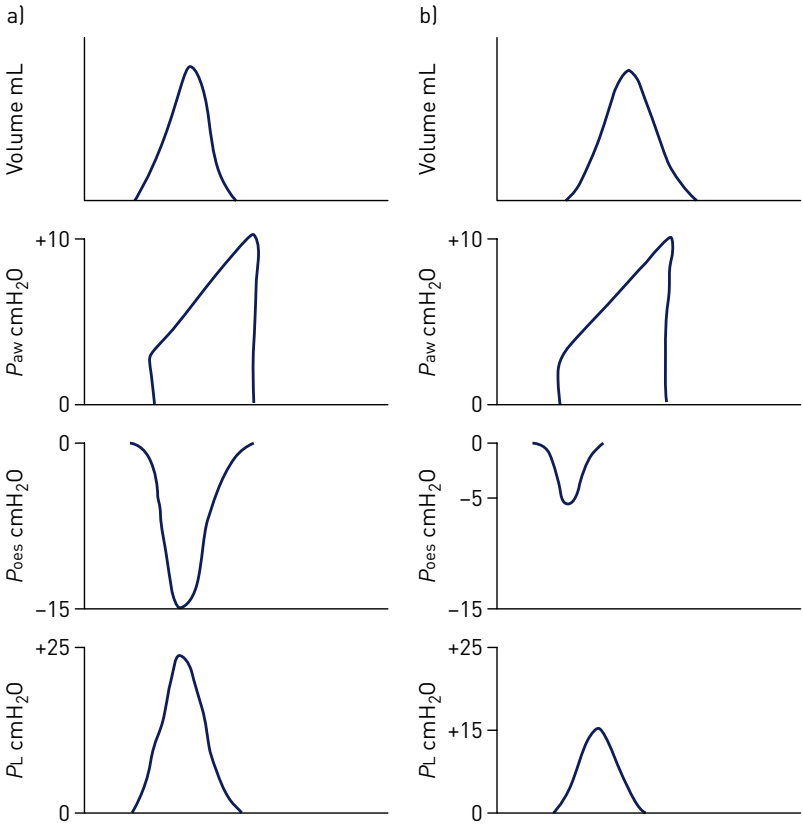


*Figure 6. Pressure support ventilation in a) a patient with marked respiratory distress and b) a patient with no respiratory distress. In a)* $P_L = P_{aw} - P_{oes} = 10\ cmH_2O - (-15\ cmH_2O) = 25\ cmH_2O$, *in b)* $P_L = P_{aw} - P_{oes} = 10\ cmH_2O - (-5\ cmH_2O) = 15\ cmH_2O$.

with increased mortality, even when protective invasive ventilation is applied. In fact, keeping the $\Delta P$ value under 14 cmH$_2$O significantly increases survival.

*Mechanical power* Different mechanical variables have been shown to contribute to VILI. These variables ($V_T$, $P_{plat}$, $\Delta P$, PEEP, flow and respiratory rate) have been addressed separately in previous studies.

The mechanical power equation unifies the variables known to be related to development of VILI:

$$\text{Power}_{rs} = RR \cdot \left\{ \Delta V^2 \cdot \left[ \frac{1}{2} \cdot EL_{rs} + RR \cdot \frac{(1+I{:}E)}{60 \cdot I{:}E} \cdot R_{aw} \right] + \Delta V \cdot PEEP \right\} \quad (4)$$

where RR is the respiratory rate, $\Delta V$ is the change in volume, $EL_{rs}$ is the elastance of the respiratory system, I:E is the inspiratory to expiratory ratio and $R_{aw}$ is the airway resistance.

This equation focuses on the concept that changing one single variable may not be sufficient to prevent VILI if the value of mechanical power is not changing. For example, a reduction in $V_T$ may not be sufficient if simultaneously requiring an increase of respiratory rate in order to maintain an adequate minute ventilation. Changing $V_T$, $\Delta P$ and inspiratory flow produce an exponential increase in mechanical power (factor=2). A higher respiratory rate increases mechanical power value with an exponent of 1.4, while a higher PEEP produces a linear increment of mechanical power. Although, to date, the mechanical power has been mainly studied in experimental settings, it is promising and may have important clinical implications. Although a threshold value for mechanical power in humans has still to be identified and RCTs on mechanical power are lacking, this approach helps the clinician in considering the many damage factors, which are often neglected when setting protective ventilation.

## Further reading


- Akoumianaki E, *et al.* (2014). The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med*; 189: 520–531.
- Amato MB, *et al.* (2015). Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*; 372: 747–755.
- Beitler JR, *et al.* (2019). Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure–guided strategy vs an empirical high PEEP-$F_{IO_2}$ strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome. a randomized clinical trial. *JAMA*; 321: 846–857.
- Briel M, *et al.* (2010). Higher *vs* lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*; 303: 865–873.
- Chiumello D, *et al.* (2014). The assessment of transpulmonary pressure in mechanically ventilated ARDS patients. *Intensive Care Med*; 40: 1670–1678.
- Dos Santos CC, *et al.* (2000). Invited review: mechanisms of ventilator-induced lung injury: a perspective. *J Appl Physiol (1985)*; 89: 1645–1655.
- Fan E, *et al.* (2017). An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*; 195: 1253–1263.
- Gattinoni L, *et al.* (2016). Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med*; 42: 1567–1575.
- Mauri T, *et al.* (2016). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med*; 42: 1360–1373.
- Pesenti A, *et al.* (1991). The effects of positive end-expiratory pressure on respiratory resistance in patients with the adult respiratory distress syndrome and in normal anesthetized subjects. *Am Rev Respir Dis*; 144: 101–107.

- Ricard JD, *et al.* (2002). Ventilator-induced lung injury. *Curr Opin Crit Care*; 8: 12–20.
- Rittayamai N, *et al.* (2015). Pressure-controlled *vs* volume-controlled ventilation in acute respiratory failure: a physiology-based narrative and systematic review. *Chest*; 148: 340–355.
- Sahetya SK, *et al.* (2017). Setting positive end-expiratory pressure in acute respiratory distress syndrome. *Am J Respir Crit Care Med*; 195: 1429–1438.
- Silva PL, *et al.* (2015). Mechanisms of ventilator-induced lung injury in healthy lungs. *Best Pract Res Clin Anaesthesiol*; 29: 301–313.
- Slutsky AS, *et al.* (2014). Ventilator-induced lung injury. *N Engl J Med*; 370: 980.
- Terragni P, *et al.* (2016). Dynamic airway pressure-time curve profile (stress index): a systematic review. *Minerva Anestesiol*; 82: 58–68.
- Terragni PP, *et al.* (2013). Accuracy of plateau pressure and stress index to identify injurious ventilation in patients with acute respiratory distress syndrome. *Anesthesiology*; 119: 880–889.
- The Acute Respiratory Distress Syndrome Network, *et al.* (2000). Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*; 342: 1301–1308.
- Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, *et al.* (2017). Effect of lung recruitment and titrated positive end- expiratory pressure (PEEP) *vs* low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*; 318: 1335–1345.

# Effects of invasive ventilation on the respiratory muscles

Annemijn H. Jonkman, Zhong-Hua Shi and Leo Heunks

A disturbance in the balance between the capacity and loading of the respiratory muscles may result in respiratory failure. For these patients, invasive ventilation is a life-saving intervention that aims to reduce the work of breathing and improve gas exchange. While invasive ventilation can partially or completely unload the respiratory muscles, respiratory muscle function may deteriorate in ventilator-bound ICU patients. Compared to peripheral skeletal muscles, the diaphragm appears more affected by critical illness and invasive ventilation. Diaphragm weakness is associated with prolonged ventilator weaning, increased risks of ICU re-admission and hospital re-admission, and mortality. Therefore, it is of crucial importance to limit the detrimental effects of critical illness and invasive ventilation on the respiratory muscles.

While the respiratory muscle pump consists of multiple inspiratory and expiratory muscles, this chapter focuses on the diaphragm, the main muscle for inspiration. We summarise the prevalence of diaphragm muscle weakness in ventilated ICU patients and potential mechanisms causing ventilator-induced diaphragm dysfunction. Clinical implications of diaphragm dysfunction are discussed, as well as monitoring techniques and potential preventive and therapeutic strategies to limit the development of diaphragm weakness.

## Definition and prevalence of diaphragm muscle weakness in ICU patients

The gold standard to assess *in vivo* diaphragm strength in ventilated patients is to measure the change in transdiaphragmatic twitch pressure induced by magnetic stimulation of the phrenic nerves ($P_{di,tw}$). This assessment provides a standardised

**Key points**

- Diaphragm weakness occurs rapidly during invasive ventilation and is associated with prolonged ventilator weaning and poor outcome.
- Prolonged low diaphragm activity can lead to disuse atrophy. Excessive respiratory muscle loading can cause diaphragm injury.
- A diaphragm-protective ventilation strategy enables a new opportunity to minimise, prevent or recover from the effects of invasive ventilation on the diaphragm.