

# Acute Respiratory Distress Syndrome (ARDS)

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# Acute Respiratory Distress Syndrome (ARDS)

## Current Status 2017

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This module is updated and maintained by the (ARF) section

Latest Update

Second Edition

## Acute Respiratory Failure

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## Learning Objectives

After studying this module on Respiratory failure, you should be able to:

- Understand the current Berlin definition for ARDS
- Understand the relationships between the Berlin definition of ARDS and the lung histology during ARDS

- Know which key respiratory mechanics variables should be monitored and how
- Know advanced monitoring of the lung function during mechanical ventilation for ARDS
- Know the rationale and the practical issues of setting the ventilator in ARDS patients
- Know the rationale and the practical issues of setting adjunct therapies in ARDS patients

## eModule Information

**COBATrICe competencies covered in this module:**

### Competencies

- Adopts a structured and timely approach to the recognition, assessment and stabilisation of the acutely ill patient with disordered physiology
- Obtains and interprets the results from blood gas samples
- Manages the care of the critically ill patient with specific acute medical conditions
- Recognises and manages the patient with acute respiratory failure and ARDS
- Manages sedation and neuromuscular blockade

### Faculty Disclosures:

The authors of this module have not reported any disclosures.

**Duration:** 7 hours

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# 1. Introduction

Acute respiratory failure (ARF) is one of the most frequent reasons for admission to the intensive care unit (ICU) and is associated with significant mortality. Acute respiratory failure frequently progresses to acute respiratory distress syndrome (ARDS). Here, we will focus on ARDS, the most severe form of hypoxemic ARF, and particularly on those ARDS patients requiring ventilatory support and mechanical ventilation. Among all patients admitted to ICU with ARF, almost three-quarters meet the criteria for ARDS ([Bellani et al. 2016](#)).

ARDS is not a disease in itself but a clinical syndrome precipitated by a large variety of clinical conditions, such as pneumonia, sepsis, trauma, massive pulmonary embolism, aspiration, and thus, in addition to the management of ARDS, treatment of the underlying disease is crucial.



## References

- [Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; LUNG SAFE Investigators; ESICM Trials Group., Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries., 2016, PMID:26903337](#)

## 2. Definition and Incidence Of ARDS

In 1967, Ashbaugh and colleagues reported the clinical characteristics of 12 patients with sudden respiratory failure that they called ARDS (Ashbaugh et al. 1967). None of these patients had underlying cardiac or pulmonary disease, and rapidly developed acute hypoxemia, stiff lungs, and diffuse bilateral alveolar infiltrates on chest x-ray a few days following exposure to a precipitating factor. Outcomes were poor with 7 of the 12 patients dying. Autopsies revealed a characteristic histological pattern of diffuse alveolar damage (DAD) including hyaline membrane formation, oedema, cell necrosis, or fibrosis (Ashbaugh et al. 1967). In 1971, Petty and Ashbaugh described the principles of ARDS management which revolved around mechanical ventilation using a high fractional inspired oxygen concentration ( $FiO_2$ ) and positive end-expiratory pressure (PEEP) (Petty and Ashbaugh. 1971). In 1994, an international American–European Consensus Conference (AECC) proposed the first definition of ARDS (Bernard et al. 1994) using the four following criteria:

1. acute onset of hypoxemia,
2.  $PaO_2$  to  $FiO_2$  ratio  $\leq$  200 mmHg regardless of PEEP level,
3. presence of bilateral infiltrates on chest radiograph, and
4. pulmonary artery wedge pressure  $\leq$  18 mmHg or no clinical signs of cardiogenic pulmonary oedema (Bernard et al. 1994).



### Notes

- ARDS was first described by Ashbaugh and colleagues in 1967
- At autopsy, diffuse alveolar damage was seen in almost all deceased patients
- The first clinical definition was established in 1994

Patients meeting all these criteria but less severe hypoxemia ( $PaO_2$  to  $FiO_2$  ratio between 201 and 300 mmHg) were considered to have acute lung injury (ALI) and not ARDS. However, this clinical definition was much criticized (Phua, Stewart and Ferguson. 2008) leading to the establishment of the current Berlin Definition in 2011 (ARDS Definition Task et al. 2012)



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- ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS., Acute respiratory distress syndrome: the Berlin Definition., 2012, PMID:22797452

## 2. 1. The current Berlin definition

The Berlin definition sought to address the limitations of the AECC criteria and to classify patients according to severity of ARDS. An expanded rationale was then published proposing treatments and ventilatory management strategies according to the degree of hypoxemia (Ferguson et al. 2012) . The changes proposed in the Berlin definition were as follows:

- “Acute onset” of ARDS is defined as respiratory symptoms occurring within 7 days of a clinical insult.
- Patients are stratified according to the severity of hypoxemia, and classified as mild, moderate and severe ARDS when PaO<sub>2</sub>/FiO<sub>2</sub> ratio is between 201 and 300, 101 and 200, and equal to or below 100 mmHg, respectively (ARDS Definition Task et al. 2012) . By including patients with a PaO<sub>2</sub> /FiO<sub>2</sub> ratio up to 300 mm Hg, the Berlin definition now encompasses those patients with mild ARDS formerly named acute lung injury. Based on several previous studies, oxygenation criteria were well-correlated to severity with mortality of 27, 32, and 45% in mild, moderate and severe ARDS respectively.
- As a major limitation of the AECC definition was assessment of PaO<sub>2</sub> /FiO<sub>2</sub> ratio regardless of the PEEP level used, the Berlin definition stated that PaO<sub>2</sub>/FiO<sub>2</sub> ratio had to be measured with a PEEP level of at least 5 cmH<sub>2</sub> O (ARDS Definition Task et al. 2012) . The AECC definition considered that pulmonary arterial wedge pressure should not exceed 18 mm Hg in ARDS (Bernard et al. 1994) . However, high values of pulmonary wedge pressure are commonly observed in patients with ARDS (Ferguson et al. 2012) and the use of pulmonary artery catheter is no longer routine practice for hemodynamic management ( Wheeler et al. 2006; Richard et al. 2003) . Therefore, pulmonary artery wedge pressure requirement was not included in the Berlin definition and it was stated that respiratory failure must not be fully explained by cardiac failure or fluid overload as judged by the clinician or confirmed by echocardiography(ARDS Definition Task et al. 2012) .
- The Berlin definition considered radiological abnormalities as bilateral opacities on chest-X-ray but also on CT-scan, which should furthermore not be fully explained by pleural effusions, lobar or lung collapse or nodules(ARDS Definition Task et al. 2012) . The Berlin definition proposed an educational course to classify ARDS as consistent, equivocal, or inconsistent based on chest-X-ray (ARDS Definition Task et al. 2012) . However, the radiographic diagnostic accuracy and inter-rater agreement remain poor using chest-X-ray, even after educational training(Peng et al. 2017) .

### Notes

- The current definition of ARDS is the Berlin definition (established at the annual meeting of the European Society of Intensive Care Medicine held in Berlin in 2011).
- Mortality increases with severity of hypoxemia (mild, moderate or severe)
- The recognition of ARDS on chest radiograph is challenging and there is considerable inter-observer variability.

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## 2. 2. Limitations of the current definition

A major limitation is that severity can be assessed on a single blood gas measurement without prior standardization of ventilator settings including PEEP which may have a major influence on oxygenation. In three Randomized Controlled Trials (RCTs) that have compared two levels of PEEP (lower vs. higher), oxygenation was always better in the higher-PEEP group than in the lower-PEEP group. After optimizing ventilator settings and increasing the PEEP level, several studies have shown that a high proportion of patients would have their severity modified based on the  $\text{PaO}_2/\text{FiO}_2$  ratio, from severe to moderate/mild, or from moderate to mild (Ferguson et al. 2004; Villar et al. 2013; Villar et al. 2007).  $\text{FiO}_2$  variations may also be associated with significant changes in  $\text{PaO}_2/\text{FiO}_2$  ratio (Ferguson et al. 2004; Aboab et al. 2006), and it has been shown that for the same  $\text{PaO}_2/\text{FiO}_2$  ratio, patients ventilated with a higher  $\text{FiO}_2$  had a higher mortality than those ventilated with a lower  $\text{FiO}_2$  (Britos et al. 2011) .

To standardize disease severity, ventilator settings should probably be optimized using tidal volumes (VT) of approximately 6 ml/kg of predicted body weight and a high PEEP level. Indeed, it has been shown that mortality was more reliably predicted according to the three categories of severity when  $\text{PaO}_2/\text{FiO}_2$  ratio was measured with a PEEP level of at least 10 cm H<sub>2</sub>O and  $\text{FiO}_2$  at least 0.5 (Villar et al. 2013; Villar et al. 2007). Likewise, the time interval between optimizing ventilator settings and measuring the  $\text{PaO}_2/\text{FiO}_2$  ratio could be crucial: assessment of the

PaO<sub>2</sub>/FiO<sub>2</sub> ratio yielded a more clinically relevant ARDS classification when measured 24 hours after ARDS onset than immediately after FiO<sub>2</sub> and PEEP settings (Villar et al. 2013; Villar et al. 2007) . The importance of accurately defining severe ARDS was illustrated by the inclusion criteria used in the PROSEVA trial. Patients were deemed eligible for inclusion only if the PaO<sub>2</sub>/FiO<sub>2</sub> ratio remained less than 150mmHg after optimization of ventilator setting and waiting 12 hours. The study subsequently revealed a mortality benefit for patients with severe ARDS managed in the prone position which may not have been found if those with mild to moderate disease had also been included by too early recruitment (Guérin et al. 2013) .

#### Notes

- The level of PEEP set by the clinician may have a major influence on oxygenation
- A major limitation of the ARDS Berlin definition is that ARDS severity can be assessed by a single blood gas measurement without prior standardization of ventilator settings.

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## 2. 3. Aetiologies and risk factors for ARDS

ARDS is an acute inflammatory lung condition and not a disease and therefore is always precipitated by an underlying process. The pulmonary inflammation may be caused by a pulmonary or an extra-pulmonary lung injury. Pulmonary ARDS is a direct insult to the lung

affecting alveolar epithelium whilst extra-pulmonary ARDS is an indirect lung injury caused by inflammatory mediators acting on the vascular endothelium (Pelosi et al. 2003; Tremblay et al. 1997).

- Pulmonary ARDS can be caused by: pneumonia (bacterial, viral, fungal), aspiration of gastric content, inhalational injury, pulmonary contusion, pulmonary vasculitis, or near drowning.
- Extra-pulmonary ARDS can be caused by: non-pulmonary sepsis, non-cardiogenic shock, pancreatitis, major trauma, multiple transfusion or transfusion-related acute lung injury, severe burns, or drug overdose.

Pulmonary ARDS is markedly more frequent than extra-pulmonary ARDS, with pneumonia being the main cause (60% of cases)(Bellani et al. 2016) . The proportion of pulmonary and extra-pulmonary lung injury depend on the higher incidence of extra-pulmonary causes amongst postoperative and trauma patients, and a higher incidence of pulmonary causes in medical patients. ARDS could also be mixed in origin; for example, a patient originally presenting with peritonitis could develop aspiration or nosocomial pneumonia and pulmonary contusion caused by major trauma could be complicated by the need for multiple transfusions(Callister and Evans 2002) . Whatever the underlying cause of ARDS, experimental studies have shown that lung injury may be exacerbated by non-protective mechanical ventilation using high VTs (greater than 12 ml/kg) and low levels of PEEP (roughly 5 cmH<sub>2</sub>O)(de Prost et al. 2011; Dreyfuss and Saumon. 1998; Dreyfuss, Soler and Saumon. 1995; Dreyfuss and Saumon. 1993; Dreyfuss et al. 1988; Slutsky and Tremblay. 1998).

By definition, respiratory symptoms must commence within 7 days of a clinical insult. Accurately timing the onset enables the clinician to eliminate some respiratory diseases from the differential diagnosis. Disease processes developing over several weeks include idiopathic pulmonary fibrosis, nonspecific interstitial pneumonitis and granulomatosis with polyangitis (Guérin, Thompson and Brower. 2015). By contrast, many diseases with acute onset may mimic ARDS such as alveolar hemorrhage due to vasculitis, drug-induced pulmonary toxicity, acute eosinophilic pneumonia, organizing or diffuse interstitial pneumonia, and in rare cases cancer infiltration(Guérin, Thompson and Brower. 2015; Gibelin et al. 2016) . Because these diseases may fit the definition of ARDS, a complete diagnostic workup should include bronchoalveolar lavage including fluid for cytology and chest CT scan in order to identify patients who might benefit from specific therapies including corticosteroids.

#### Notes

- ARDS can be caused by a pulmonary injury (direct insult affecting alveolar epithelium) or an extra-pulmonary injury (indirect insult affecting vascular endothelium)
- Pneumonia is the main cause of ARDS

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## 2. 4. Incidence of ARDS in the ICU

The incidence of ARDS obviously depends on the definition used and will be higher using the Berlin definition - which includes patients with a PaO<sub>2</sub> /FiO<sub>2</sub> ratio up to 300 mmHg - than using the AECC definition. At the beginning of the 2000s, three studies assessed incidence and outcomes for patients with ARDS using the AECC definition (Bersten et al. 2002; Brun-Buisson et al. 2004; Rubenfeld et al. 2005) (Bersten AD et al. 2002; Brun-Buisson C et al. 2004; Rubenfeld GD et al. 2005). In these studies, around 7 to 8% of the patients admitted to the ICU met clinical criteria for ARDS. In the recent LUNG SAFE study performed in 2014 among 459 ICUs in 50 countries over a 4-week period patients with ARDS represented 10% of all ICU admissions and 23% of all intubated patients in ICU (Bellani et al. 2016) . Among them, 30% had mild, 47% had moderate, and 23% had severe ARDS. The triggers for ARDS were: pneumonia in 59%, aspiration in 14%, extra-pulmonary sepsis in 16%, and non-cardiogenic shock in 7.5% of cases. Whereas some patients may have several risk factors, some patients may have ARDS without any of the usual risk factor. This study also highlighted the fact that many clinicians did not identify those patients with ARDS. In mild ARDS, this was the case in almost half of the patients. Clinical recognition of ARDS was better for severe ARDS, but still undiagnosed in 21% of the cases. Moreover, clinician recognition of ARDS at the time of fulfillment of clinical criteria was only 34%, suggesting that diagnosis was frequently delayed.

## Notes

- Around 10% of patients admitted to the ICU and 23% of intubated patients meet the criteria for ARDS
- Almost half of the patients with ARDS have moderate hypoxemia (between 100 and 200 mm Hg)
- A diagnosis of ARDS is not made in a high proportion of patients with the condition

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### 3. Pathophysiology of ARDS From Histological Lesions to Baby Lung with Hypoxemia

Although not part of the current definition, ARDS is characterized by a marked reduction in lung compliance (Ashbaugh et al. 1967). This is related to DAD which is considered the morphological hallmark of the lung in ARDS (Katzenstein, Bloor and Leibow. 1976; Tomashefski JF 2000).



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#### 3. 1. Histological lesions in ARDS and the time course of pathological findings

Diffuse alveolar damage is defined by the presence of hyaline membranes associated with interstitial oedema, cell necrosis and proliferation and then fibrosis at a later stage (Katzenstein, Bloor and Leibow. 1976; Tomashefski JF 2000) (Figure 1). It has generally been assumed that these changes evolve over time and in different phases (exudative, proliferative and fibrosis) characterized by specific morphological changes. The exudative phase features capillary congestion and intra-alveolar oedema and is maximal during the earliest stages. The second phase- the proliferative phase - is marked by intense cellular proliferation of alveolar type 2 cells and fibroblasts. This phase can result in resolution leading to the formation of normal tissue or disease progression leading to fibrosis, especially if lung injury is persistent. These proposed sequential changes may overlap and fibrosis may occur early in the course of ARDS.

Whatever the origin of ARDS, DAD is considered the morphological hallmark (Katzenstein, Bloor and Leibow. 1976; Tomashefski JF 2000). However, its incidence is highly variable from one study to another and largely depends on the type of examination: autopsy (Thille et al. 2013; Sarmiento et al. 2011) or open lung biopsy (Guerin et al. 2015; Kao et al. 2015; Papazian et al. 2007). In an analysis of 356 patients with ARDS undergoing autopsy the overall incidence of DAD was 45% (Thille et al. 2013). As hyaline membranes may be delayed by 2 to 3 days (Katzenstein, Bloor and Leibow. 1976) the incidence of DAD was significantly higher in patients with ARDS for more than 72 hours. The proportion of patients with DAD also increased with severity. The incidence was: 12, 40, and 58% for patients with mild, moderate, and severe ARDS, respectively (Thille et al. 2013). Whereas almost all patients with DAD found at autopsy met the clinical criteria set out by the Berlin definition for ARDS (high sensitivity), less than half of all patients with ARDS had DAD (low specificity). The low specificity of the Berlin definition in DAD detection could be attributed to the presence of other processes with a similar clinical picture.

On the other hand, it should be noted that the presence of DAD could be associated with higher mortality as compared to patients without DAD (Cardinal-Fernández et al. 2016). Unfortunately, to date, no biomarkers exist to identify DAD amongst patients with ARDS and clinical factors have too low predictive value to help the clinician at the bedside (Lorente et al. 2015).

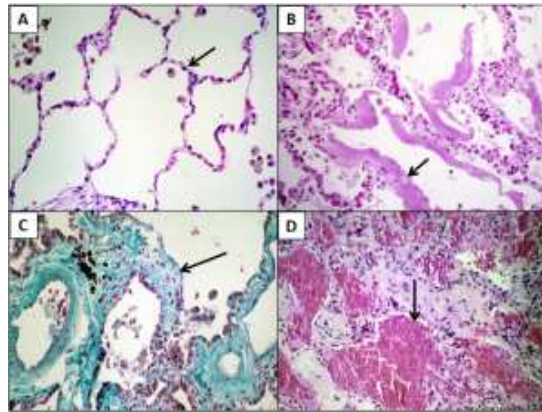


Figure 1: Histological findings in patients with or without acute respiratory distress syndrome (ARDS)

### Figure 1:

A: Normal lung tissue characterized by a thin alveolar-capillary membrane (arrow) separating red blood cells from the alveolar space, and including endothelial cell, basal membrane and epithelial cell.

B: Typical histological findings of diffuse alveolar damage (DAD) with hyaline membranes (arrow) covering the denuded basal membrane and necrosis of alveolar type I cells, illustrating the morphological hallmark of the ARDS.

C: Fibrosis of the alveolar-capillary membrane in green (arrow).

D: The last panel shows histological criteria for the diagnosis of alveolar hemorrhage including the presence of intense hemosiderin infiltration in the intra-alveolar spaces (arrow). Although no clinical criteria allow for the differentiation of the two diagnoses, microscopic analysis of the lungs can easily differentiate alveolar hemorrhage or pneumonia from ARDS, characterized by typical lesions of hyaline membranes.

### Notes

- Although DAD is considered the morphological hallmark of the ARDS lung, only half of the patients with ARDS exhibit DAD at histological examination
- Patients with DAD may have higher mortality than those without DAD

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### 3. 2. The concept of "baby lung"

By comparing the measurement of compliance and the distribution of lung aeration compartments on the CT scan, Gattinoni found that compliance correlated with the normally aerated lung and that the specific compliance (compliance divided by functional residual capacity) was actually normal. This led to the concept of baby lung along which the amount of aerated lung in ARDS is that of a lung of a baby. The "baby lung" is a physiological concept meaning that due to the large amount of non-aerated lung the remaining normally aerated lung accessible to ventilation is considerably reduced and of similar size as that of a baby (Gattinoni and Pesenti. 2005) . Consequently, the lung compliance is markedly reduced and linearly related to the "baby lung" dimensions, suggesting that the ARDS lung is not "stiff" but instead small, with nearly normal intrinsic elasticity. Therefore, if the baby lung is reduced by two third the size of tidal volume should be reduced as much.

#### Notes

- Baby lung is not a stiff lung but a small lung with normal elasticity

#### References

### 3. 3. Mechanisms of hypoxemia in ARDS

Several mechanisms contribute to the development of hypoxemia in ARDS. It is primarily caused by the loss of lung volume due to alveolar oedema and collapse leading to intrapulmonary shunt and marked alteration in ventilation-to-perfusion distribution (VA/Q ratio). Surfactant deficiency and impairment to the hypoxic pulmonary vasoconstriction response also contribute to hypoxemia. Other factors can induce or worsen oxygenation. Firstly, Pulmonary hypertension and positive pressure ventilation can open a patent foramen ovale leading to the formation of an intracardiac shunt. Right-to-left shunting across a patent foramen ovale can be detected in around 20% of patients with ARDS; these patients have a poor oxygenation response to increased PEEP ([Mekontso Dessap et al. 2010](#)) . Secondly, an increase in the physiological dead space occurs due to abnormalities in pulmonary blood flow to lung regions that remain well ventilated ([Ralph et al. 1985](#); [Nuckton et al. 2002](#)). This leads to both hypoxemia and hypercapnia. In a prospective observational study, large dead space in the early course of ARDS was associated with increased mortality([Nuckton et al. 2002](#)) . Thirdly, lung diffusion for carbon oxide alteration may also, marginally, contribute to hypoxemia ([Di Marco et al. 2010](#)) . Impairment in diffusion of carbon dioxide and oxygen is caused by interstitial edema, hyaline membrane and fibrosis thickening the alveolo-capillary membrane. Finally, a low mixed venous oxygen saturation caused by a low cardiac output state will further worsen hypoxemia because lung function cannot reliably replenish the arterial saturations for all the reasons already highlighted([Takala 2007](#)) .



#### Notes

- In ARDS, hypoxemia is predominantly caused by increased volumes of non-aerated perfused lung
- Other mechanisms contributing to hypoxemia include intracardiac shunt across a patent foramen ovale, increased physiological dead space, altered lung diffusion across alveolo-capillary membrane and increased venous admixture.



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## 4. Mechanical Ventilation

### 4. 1. Ventilator induced lung injury

The primary goal of mechanical ventilation is to prevent ventilator-induced lung injury (VILI). However, VILI has different components. The most important is the excess in end-inspiratory lung volume and is named volutrauma. Actually, what is important is the strain, ie the ratio of VT to the end expiratory lung volume (including that due to PEEP). The excess in strain results from the amount of not aerated lung in association with high VT and/or high volume due to PEEP and brings the end expiratory lung volume close to total lung capacity. The second mechanism of VILI is the barotrauma. Indeed, there is linear relationship between the strain and the resulting stress, which is the trans-pulmonary pressure. The third component is atelectrauma which is due to the repeated opening and closing of small airways over the breathing cycles. This phenomenon may cause further inflammation into the lung and may be associated with huge local trans-pulmonary pressure at the interface of such lung regions and those which remained closed. The cellular toxicity of oxygen is also a component of VILI. The bio trauma is the overall biological response that wraps up the mechanotransduction due to the effect of stress and strain at the cellular level. Unlike spontaneous breathing, mechanical ventilation delivers positive pressure throughout the respiratory cycle. Although mechanical ventilation is needed in most cases of severe ARDS, it is well demonstrated that the use of mechanical ventilation can worsen pre-existing lung injury ([de Prost et al. 2011](#); [Dreyfuss and Saumon. 1998](#); [Dreyfuss, Soler and Saumon. 1995](#); [Dreyfuss and Saumon. 1993](#); [Dreyfuss et al. 1988](#); [Slutsky and Tremblay. 1998](#)). The ventilator settings should be adjusted to ensure adequate gas exchange without causing ventilator-induced lung injury (VILI). The two factors that promote VILI are:

1. Hyperinflation during inspiration induced by large VTs and high end-inspiratory pressures. Hyperinflation represents excessive alveolar strain defined as the ratio between VT and amount of aerated lung at the end of expiration, and may be prevented by reducing VTs and end-inspiratory plateau pressure.
2. Alveolar collapse during expiration and repeated alveolar opening and closing during each breath promoted by low pressures during expiration. This phenomenon (atelectrauma) is quantitatively defined as the amount of collapsed lung tissue re-expansion during inspiration and recollapsing during subsequent expiration and may be prevented by applying higher PEEP level.

Recently, it has been shown that driving pressure (plateau pressure – PEEP) was a major determinant of outcome ([Amato et al. 2015](#); [Amato et al. 1998](#); [Guérin et al. 2016](#)). In addition, , it has been suggested that the mechanical power transferred to the respiratory system from the ventilator plays a key factor in VILI ([Tonetti et al. 2017](#)) . This means that not only the strain (change in lung volume) but both high flow and respiratory rate are potentially harmful to the lungs.

- Mechanical ventilation can worsen pre-existing lung injury
- Ventilator-induced lung injury is mainly promoted by alveolar hyperinflation during inspiration and alveolar collapse during expiration.
- Driving pressure (plateau pressure – PEEP) is a major factor of VILI and outcome.



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## 4. 2. Targets of mechanical ventilation

The use of lung protective ventilation including low VTs, high PEEP levels and strict monitoring of plateau pressure to avoid exceeding 30 cm H<sub>2</sub>O is the cornerstone of current recommendations regarding mechanical ventilation in patients with ARDS (Ferguson et al. 2012). The main objective is to achieve adequate gas exchange whilst avoiding VILI. The gas exchange targets are not clearly defined. It is common practice to target a PaO<sub>2</sub> of at least 60 mm Hg and SaO<sub>2</sub> of at least 90%. In fact, no studies have shown that increasing PaO<sub>2</sub> improves outcome. By contrast, it has been suggested that targeting SpO<sub>2</sub> between 94% and 98% may improve outcomes in critically ill patients compared to conventional therapy maintaining SpO<sub>2</sub> between 97% and 100% (Girardis et al. 2016). More conservative oxygenation strategies targeting SpO<sub>2</sub> between 88% and 92% in patients under mechanical ventilation may be feasible (Panwar et al. 2016). In three randomized controlled trials comparing high PEEP versus low PEEP in ARDS, FiO<sub>2</sub> was adjusted to maintain SpO<sub>2</sub> above 88% (Meade et al. 2008; Mercat et al. 2008; Brower et al. 2004) (Meade MO et al. 2008; Mercat A et al. 2008; Brower RG et al. 2004). In these 3 studies, VT could be increased in case of respiratory acidosis when pH dropped below 7.15-7.20. Protective ventilation using low VTs may induce respiratory acidosis. Although the minimum value below which the pH must be corrected is not known, pH should usually be maintained above 7.2.

### Notes

- Lung protective ventilation including low VTs, high PEEP levels and a plateau pressure below 30 cm H<sub>2</sub>O is the main target of mechanical ventilation

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### 4. 3. Mechanical properties of the respiratory system

ARDS is characterized by low compliance, which, as discussed above, reflects loss of aeration, and high resistance of the respiratory system. In large randomized controlled studies the compliance of the respiratory system (measured as the VT divided by the driving pressure) averaged approximately 30 ml/cmH<sub>2</sub>O but values as low as 20 ml/cm H<sub>2</sub>O were measured (Grasso et al. 2002) . Resistance is usually high as a result of low lung volume(Eissa et al. 1991) . Non-negligible levels of intrinsic PEEP can occur in ARDS patients and it should be systematically monitored, especially in patients ventilated with a high respiratory rate (Koutsoukou et al. 2000; Vieillard-Baron et al. 2002) . The compliance measured at the bedside commonly includes the lung and the chest wall. Assessment of chest wall compliance and its impact on plateau pressure is possible with the measurement of oesophageal pressure. Chest wall compliance is usually markedly higher than lung compliance and so its impact on plateau pressure and driving pressure is negligible in the large majority of patients with ARDS including the obese. However, the impact of altered chest wall compliance can be relevant in patients with acute abdominal disease such as peritonitis or bowel occlusion (Ranieri et al. 1997; Mergoni et al. 1997; Gattinoni et al. 1998).

#### Notes

- ARDS is characterised by low compliance of the respiratory system (around 30 ml/cm H<sub>2</sub>O)

- The compliance measured at the bedside (VT divided by driving pressure) is the compliance of the respiratory system including the lung as well as the chest wall
- The impact of chest wall compliance on plateau pressure can be relevant in some patients, especially those with an abdominal origin of ARDS



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#### 4. 4. Oxygenation strategies to avoid intubation and criteria for intubation

The first-line strategy in supporting hypoxemic patients is to provide oxygen. There are several means for that, like oxygen mask, oxygen mask plus reservoir, high flow canula. To date, there is no strong evidence for the use of noninvasive ventilation (NIV), including continuous positive airway pressure through a face mask, in ARDS patients. Several cohort studies document intubation rates of 40-50% in cases of moderate and severe ARDS ([Antonelli et al. 2007](#); [Thille et al. 2013](#); [Bellani et al. 2016](#); [Agarwal, Aggarwal and Gupta. 2010](#)). Only one randomized controlled trial which included patients with ARDS demonstrated a decrease in intubation rate with NIV as compared to standard oxygen therapy([Ferrer et al. 2003](#)) . However, nearly 30% of the patients had cardiogenic pulmonary edema, a condition well documented to respond favorably to NIV ([Vital, Ladeira and Atallah. 2013](#)) . The main downsides of NIV are the risk of delaying intubation by masking signs of respiratory distress ([Carrillo et al. 2012](#)) or worsening VILI ([Slutsky and Ranieri. 2013](#)) The LUNG SAFE study suggested that patients with a PaO<sub>2</sub>/FiO<sub>2</sub> < 150 mm Hg treated with NIV had higher mortality than those treated with invasive mechanical ventilation ([Bellani et al. 2016](#)) . VTs delivered with NIV have been shown to be particularly large ([Carteaux et al. 2016](#)) .A further issue with NIV is patient tolerance: poor tolerance of the facemask is frequent and can lead to the subsequent requirement for intubation ([Antonelli et al. 2001](#); [Demoule et al. 2006](#)). Though tolerance is improved with a Helmet ([Antonelli et al. 2002](#); [Tonnelier et al. 2003](#)) only one single center randomized controlled trial found improved outcomes when compared to face mask NIV ([Patel et al. 2016](#)) . Although studies have assessed using low levels of pharmacological sedation in order to improve tolerance of NIV and hence avoid intubation the results have been contradictory ([Constantin et al. 2007](#); [Muriel et al. 2015](#)). More recently, a large multicenter randomized controlled trial ([Frat et al. 2015](#)) found lower mortality rates for patients treated with high-flow nasal cannula oxygen (HFNC) therapy as compared to standard oxygen or NIV. This strategy rapidly improved comfort and decreased respiratory rate, with a significantly lower intubation rate in the most severely ill patients. On this basis HFNC is recommended as a first-line strategy for oxygenation in patients with ARDS.

Whatever oxygenation strategy is used, intubation should not be delayed. There is no hard evidence as to when intubation should be performed but must be considered when the respiratory rate is above 35-40 breaths/min and there are clinical signs of respiratory distress . Severe hypoxemia defined as PaO<sub>2</sub> < 60 mm Hg or SpO<sub>2</sub> < 90% despite high FiO<sub>2</sub> , respiratory acidosis, and copious secretions are other indications for intubation. Non-respiratory indications for invasive ventilation are altered consciousness and the occurrence of shock. Indeed, the need for vasopressors, or an increase in severity scores has been found to be a strong predictor for intubation and mortality ([Antonelli et al. 2007](#); [Thille et al. 2013](#); [Carrillo et al. 2012](#); [Antonelli et al. 2001](#)).

#### Notes

- The rate of intubation in ARDS patients treated with NIV is particularly high (around 40-50%)
- NIV may be associated with worse outcomes in the most severely ill patients
- High-flow oxygen therapy is an alternative to standard oxygen or NIV
- There are no guidelines for intubation but it should not be delayed

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## 4. 5. Ventilatory mode and monitoring during invasive mechanical ventilation

Worldwide assist-control in volume-controlled ventilation (VCV) is the most commonly used mode of ventilation in ICU (Esteban et al. 2013) . However, there are no data to demonstrate a difference in outcomes between VCV and pressure-controlled ventilation (PCV) (Rittayamai et al. 2015) . Whatever the ventilator mode used, VTs and end-inspiratory plateau pressure should be limited and continuously monitored.

In terms of respiratory mechanics, the main advantage of VCV versus PCV is the continuous monitoring of plateau pressure (see below). Using PCV,  $V_T$  and minute ventilation limits must be carefully set using the ventilator alarms since reduced compliance or increased resistance will be detected by a drop of  $V_T$  . Plateau pressure can be continuously monitored during PCV by inspecting the flow signal. If end-inspiratory flow is nil the pressure set at the ventilator in PCV is the plateau pressure. If it is still positive, a resistive pressure is included, which can be calculated by performing an end-inspiratory occlusion manually. The end-inspiratory plateau pressure cannot exceed the set inspiratory pressure in PCV.



### Notes

- There are no clinical data demonstrating a difference in outcomes between VCV and PCV
- The main advantage of VCV is respiratory mechanics monitoring.



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## 4. 6. Adjustment of ventilatory settings

### 4. 6. 1. Adjustment of VT

The use of low VTs is the cornerstone of mechanical ventilation in ARDS. Ventilation with a VT of 6 ml/kg predicted body weight (PBW) has been shown to significantly decrease mortality (by 9%) when compared with ventilation with 12 ml/kg PBW VTs (Acute Respiratory Distress Syndrome et al. 2000). High VTs shortly after ARDS onset could be associated with an increased mortality (Needham et al. 2015). The evidence is strong and therefore, setting VTs at 6 ml/kg PBW as early as possible in patients with ARDS is crucial. This strategy has been assessed in several large randomized controlled trials without adverse effects (Meade et al. 2008; Mercat et al. 2008; Brower et al. 2004) and especially without the need for an increase in sedation levels (Cheng et al. 2005; Kahn et al. 2005). Even in patients without ARDS, the use of low VTs may reduce the risk of developing ARDS (Serpa Neto et al. 2012), and the current question is whether low VTs should be used in all intubated patients at risk for ARDS. The driving pressure should be monitored and directly depends on VT (and compliance). It has been shown that a high driving pressure exceeding 14 cm H<sub>2</sub>O was associated with poor outcomes, and thus, an unresolved question is to know whether or not VT should be reduced below 6 ml/kg to decrease the driving pressure. Given low VTs, the adjusted respiratory rate should usually be relatively high, around 25 breaths per minute, to avoid respiratory acidosis. Increase in respiratory rate may be deleterious via an increase in energy transfer from the ventilator to the lung. Furthermore, there is some experimental evidence that mild respiratory acidosis may protect the lung (Laffey et al. 2004).

#### 4. 6. 2. Adjustment of PEEP

In 1975, the best PEEP was the level that maximized oxygen transport whilst having the lowest degree of hemodynamic impairment (Suter, Fairley and Isenberg. 1975). It was set at the point with highest compliance and lowest alveolar dead space. PEEP was selected in many studies to target an increase in alveolar recruitment, i.e. the increase in aerated lung mass resulting from the reduction in non-or poorly aerated lung mass. It has been shown that the response to PEEP may differ according to the origin of ARDS (pulmonary vs. extra-pulmonary) (Gattinoni et al. 1998), the timing (early vs. late ARDS) (Grasso et al. 2002), the localization of infiltrates (diffuse vs. lobar) (Puybasset et al. 2000), the potential for recruitment (Gattinoni et al. 2006), or the sub phenotype characterized by particularly severe inflammation (Calfée et al. 2014). Indeed, some patients may have high potential for alveolar recruitment induced by PEEP while others have low potential (Grasso et al. 2007). Thus, a personalized approach is best, adjusting PEEP for each patient to optimize his/her alveolar recruitment. Indeed, when increasing PEEP reduces the driving pressure it indicates recruitment and is associated with improved survival (Panwar et al. 2016), however, it has been found that optimal PEEP set according to alveolar recruitment assessed by different methods resulted in a level between 11 and 16 cm H<sub>2</sub>O in patients with moderate to severe ARDS (Chiumello et al. 2014). To date, three large RCTs have compared lower versus higher PEEP levels (Meade et al. 2008; Mercat et al. 2008; Brower et al. 2004). Although none of them showed a difference in terms of mortality, the pooled meta-analysis found a better survival using higher PEEP in patients with PaO<sub>2</sub> / FiO<sub>2</sub> ratio ≤ 200 mmHg (Briel et al. 2010). Therefore, experts recommend the use of higher PEEP in patients with moderate or severe ARDS (Ferguson et al. 2012). The methods used to adjust PEEP in these trials were either to follow a PEEP/FiO<sub>2</sub> table (Meade et al. 2008; Brower et al. 2004) or to maintain plateau pressure below 28-30 cm H<sub>2</sub>O (Mercat et al. 2008). Whatever the method used, it is important to note that the mean PEEP level in the higher PEEP group was exactly the same in the 3 studies, i.e. 15 cm H<sub>2</sub>O.

#### 4. 6. 3. Adjustment of flow rate

When breaths are patient-triggered, direct peak-flow rate adjustment is the key setting in VCV. For this reason, the flow should be set directly and not from the inspiratory-to-expiratory time ratio. This latter method may favor long insufflation times and consequently insufficient flow rates. With a respiratory rate of 20 breaths per minute and a VT of 500 ml the insufflation flow rate is only 30 L/min which risks causing patient discomfort and an increase in the work of breathing (MacIntyre et al. 1997). The optimal value of peak-flow rate is likely to be better adjusted according to the patient's needs which can be estimated by carefully looking at the distortion of the airway pressure tracings on the ventilator screen, the patient's accessory muscle activation and other indexes like the occlusion pressure at 100 ms (now provided by several ventilators). Clinicians should be aware that a flow rate around 60 L/min usually suffices to meet a patient's ventilatory demand and that this setting can be used as a default value.

## Notes

- The VT should be adjusted to 6 ml/kg predicted body weight
- Given that high driving pressures have been associated with poor outcomes, an unresolved question is to know whether or not the VT should be reduced below 6 ml/kg to decrease driving pressure
- High PEEP levels around 15 cm H<sub>2</sub> O may improve survival in ARDS
- During VCV, flow rate around 60 L/min usually suffices to meet the patient's ventilatory demand and this setting can be used as a default value.

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## 5. Adjunct Therapies

### 5. 1. Sedation and neuromuscular blocking agents

The use of sedation improves patient tolerance of positive pressure ventilation and allows resting of respiratory muscles and the reduction of oxygen consumption by these muscles. However, even deep sedation cannot abolish a patient's respiratory effort and diaphragmatic activity ([Forel et al. 2006](#)). A series of studies performed by a single group found that the neuromuscular blocking agent cisatracurium used for 48 hours in ARDS patients with a PaO<sub>2</sub> /FiO<sub>2</sub> ratio less than 150 mmHg at PEEP of at least 5 cm H<sub>2</sub> O had several advantages to the use of sedation alone.

These were:

1. improved oxygenation,
2. reduced lung and systemic inflammation, and 3) improved patient survival after adjusting for confounding factors ([Papazian et al. 2010](#)). A large trial is ongoing to reassess the results of the Acurasys study.



#### Notes

- Neuromuscular blockers should be administered at an early stage in the management of patients with severe ARDS



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### 5. 2. Prone positioning

Performing invasive mechanical ventilation in the prone position in order to improve oxygenation in patients with ARDS has been advocated for almost 40 years. Oxygenation is invariably improved, sometimes dramatically. The dorsum of the lung has a larger volume than the anterior

and apical areas. Better ventilating the dorsal regions of the lung in the prone position, therefore improves ventilation, reduces intrapulmonary shunt leading to an improvement in V/Q matching. In addition, CT scans have suggested a reduced propensity to VILI with the prone position both reducing overinflation and improving recruitment (Cornejo et al. 2013). Furthermore, changing the direction of the vertical pleural pressure gradient makes the distribution of overall lung stress and strain more homogeneous. The prone position also has hemodynamic benefits. Firstly, the afterload to the failing right ventricle is reduced by improvements in PaO<sub>2</sub>, PaCO<sub>2</sub> and higher lung volumes, all of which result in lower pulmonary vascular resistance. Over and above this, the improvements in gas exchange allow reduced levels of PEEP which reduces alveolar vessel resistance and thus pulmonary pressures. Secondly, prone position may increase cardiac output in patients with preload dependence, probably as a result of better blood flow through the lungs. These mechanisms explain the survival benefits of proning patients with severe hypoxemia found in trials and meta-analyses. The prone position is the single intervention, together with lower V<sub>T</sub>, that showed benefit to improve patient outcome (Tonelli et al. 2014). The prone position, when used, in severe ARDS reduces mortality with a NNT of 6 in the specific setting of the Proseva trial (Guérin et al. 2013). The recommended PaO<sub>2</sub>:FiO<sub>2</sub> ratio threshold for commencing prone ventilation is 100 to 150 mmHg. Evidence dictates that proning should be performed as early as possible in the course of management of these patients and sessions should last a minimum of 16 consecutive hours. Proning should be continued until oxygenation is much improved: in the Proseva trial proning was discontinued once the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was > 150 mmHg with PEEP less than 10 cm H<sub>2</sub>O and FiO<sub>2</sub> less than 0.60 when nursed in the supine position for 4 hours (Guérin et al. 2013). The potential complications of proning including accidental extubation, vascular access problems and pressure ulcers can be significantly reduced by team experience. The primary contraindication to the use of the prone position is an unstable spine injury.



#### Notes

- The prone position should be used as early as possible in the course of management of patients with ARDS and a PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 100-150 mmHg for long sessions in centres with expertise in the procedure



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### 5. 3. Recruitment maneuvers

Recruitment manoeuvres consist of transient increases in trans-pulmonary pressure in an attempt to open collapsed alveoli. When performing a recruitment manoeuvre the pressure reached at the end of inspiration surpasses the recommended safety thresholds for short time periods. There are various mechanisms by which a recruitment manoeuvre can be performed including sigh breaths, extended sigh breaths, increased inspiratory pressures and PEEP, sustained inflation and the Staircase Recruitment Manoeuvre. There is currently minimal evidence to recommend a particular method of recruitment. At present recruitment manoeuvres cannot be recommended as part of the routine management of patients with ARDS for several reasons. These are :

1. Oxygenation benefits may be short-lived and of uncertain significance,
2. There are no studies showing patient outcome benefits,
3. It is uncertain how to differentiate responders from non-responders,
4. There is no evidence for when, how often they should be performed,
5. There is no evidence of reducing VILI ,
6. The ART trial found increased mortality with staircase recruitment manoeuvre. Experts made recently a conditional recommendation for using recruitment maneuver ([Fan et al. 2017](#)). However, since this report, a large trial using recruitment manoeuvre followed by a decremental PEEP trial to select the PEEP associated with the highest compliance was harmful to patient outcome([Cavalcanti et al. 2017](#)) .

Thus, recruitment manoeuvres may be considered as a rescue therapy but the clinician should be aware that there is no clear evidence for its benefit. The mode of recruitment used should be that with which the caregiver is familiar.



#### Notes

- Recruitment maneuvers can be considered in the most severely hypoxemic patients
- No single method can be recommended.



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The current indications for veno-venous extracorporeal membrane oxygenation (ECMO) in ARDS are severe hypoxemia ( $\text{PaO}_2/\text{FiO}_2 < 80$  mmHg on  $\text{FiO}_2$  0.9 or greater) where other methods of improving oxygenation have been not been successful; severe  $\text{CO}_2$  retention ( $\text{PaCO}_2 > 80$  mmHg); severe barotrauma with air leak; or when a safe inflation pressures (Plateau pressure  $\leq 30$  cmH<sub>2</sub>O) cannot be achieved (Combes et al. 2017). Outcomes are improved the shorter the duration of ventilation prior to initiation of ECMO. It is therefore essential to discuss cases with an ECMO centre at an early stage if lung protective ventilation is not being achieved. The veno-venous access is commonly performed via a double-lumen catheter draining blood from the vena cava to the oxygenator and via a pump in the circuit returning the oxygenated blood to the right atrium, but two-catheter methods are also used. In theory, about 400 ml  $\text{O}_2$ /min can be transferred from the oxygenator to the blood with a blood flow of up to 6 l/min. The outcomes for patients treated with pulmonary conditions are very good (60-70% survival), particularly in high volume centers. Even if it is still not clear whether ECMO has survival benefit in severe ARDS (Peek et al. 2009), prompt consideration of ECMO and discussion with an ECMO centre should take place regarding all suitable patients who are difficult to oxygenate with conventional strategies.

#### Notes

- If ECMO is considered an ECMO centre should be contacted at the earliest opportunity

#### References

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## 5. 5. Extracorporeal CO removal (ECCO R)

This method of extracorporeal support is similar to veno-venous ECMO but uses smaller intravenous access catheters. Rates of  $\text{CO}_2$  clearance of 150-200 ml /min can be achieved with a veno-venous blood flows of between 1000-2000 ml/min. ECCO<sub>2</sub> R can therefore be used to assist ultra-protective ventilation in ARDS (Terragni et al. 2009) and in some COPD patients as a substitute for invasive or non-invasive ventilation (Terragni, Faggiano and Ranieri. 2014). Although, in small studies this method has been shown to reduce cytokine production, there is still no evidence that its use in ARDS will improve survival (Taccone et al. 2017).

#### Notes

- ECCO<sub>2</sub> R is still experimental and should only be performed in dedicated centres or as part of research studies



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## 5. 6. High Frequency Oscillatory Ventilation

High Frequency Oscillatory Ventilation is a specialised mode of ventilation whereby a constant mean airway pressure is augmented by oscillating pressure variations at very high rates of up to 900 cycles per minute. Theoretically, this increases end expiratory lung volumes preventing derecruitment whilst also avoiding overdistension. Recent trials however, revealed either no benefit (Young et al. 2013) or an increased mortality using this ventilator mode (Ferguson et al. 2013). For this reason it cannot be recommended in ARDS patients.



## Notes

- HFOV should not be used in ARDS patients



## References

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## 5. 7. Nitric oxide (pulmonary vasoactive agents)

Inhaled nitric oxide (iNO) selectively dilates pulmonary vessels within aerated, ventilated lung. If hypoxic pulmonary vasoconstriction is preserved iNO can improve oxygenation and reduce pulmonary vascular resistance. Unfortunately, trials have not shown benefit with regards patient outcomes and there is a signal of increased risk of acute kidney injury. However, trials were performed before the modern era of lung protective ventilation, neuromuscular blocking agents and prone positioning.

## Notes

- iNO cannot be recommended for routine use in patients with ARDS based on currently available evidence

## 5. 8. Steroids and anti inflammatory agents

No large randomized controlled trial on the use of anti-inflammatory agents in ARDS has been shown to improve patient outcomes. Clear indications for steroid therapy for diseases that may mimic ARDS include alveolar hemorrhage due to vasculitis, drug-induced toxic pneumonia with a lymphocytic pattern, organized pneumonia and acute eosinophilic pneumonia (Guérin, Thompson and Brower. 2015; Gibelin et al. 2016). This emphasises the importance of a full diagnostic work-up for all patients with presumed ARDS. The use of steroids in ARDS is unresolved; this may be because both the timing and dose of therapy are important. In a large randomised controlled study, mortality was significantly higher when steroid therapy was started 2 weeks after the onset of symptoms whereas mortality tended to be lower in patients with signs of active proliferation (Steinberg et al. 2006). It may be that steroids are more efficient at reversing the inflammatory process in early ARDS but are ineffective once fibrosis is established. Indeed, fibrosis can be observed at day 7 (Thille et al. 2013). Most studies showing beneficial outcomes started low dose steroids early in the course of the disease process (Annane, Sébille and Bellissant E; Ger-Inf-05 Study. 2006; Meduri et al. 1998; Meduri et al. 2007). Experimental studies have also found that steroids modified respiratory mechanics and lung histology when started at an early stage (Rocco et al. 2003; Silva et al. 2009). By contrast, administration of high doses of steroids has been associated with either worse outcomes (Bone et al. 1987) or no benefit (Bernard et al. 1987).

More recently, a small study assessing the efficacy of intravenous interferon used early in the course of ARDS as a means of decreasing pulmonary vascular leakage found a survival benefit (Bellingan et al. 2014). Though too small to provide conclusive evidence further trials are ongoing.

## Notes

- There is currently no evidence for benefit of using steroids in ARDS
- Steroids have deleterious effects when administered at high doses or late in the course of ARDS

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## 5. 9. Fluid balance management

Fluid resuscitation is necessary in the early management of septic shock (Boissier et al. 2017), however, fluid overload is associated with delayed weaning from mechanical ventilation. In ARDS, a conservative fluid management strategy improved both lung function and shortened the duration of mechanical ventilation (National et al. 2006). A recent sub analysis however, has suggested that the benefits of this strategy may be limited to patients with severe inflammatory ARDS; others may suffer the side-effect of cognitive impairment (Famous et al. 2017).

### Notes

- Fluid overload should be avoided in ARDS



## References

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## 6. Spontaneous Ventilation During Mechanical Ventilation

### 6. 1. When to start spontaneous breathing?

Complete inactivity of the diaphragm may rapidly induce marked muscle atrophy and impairment of contractile force ([Jaber et al. 2011](#); [Levine et al. 2008](#)).

Airway pressure released ventilation (APRV) is a mode of ventilation combining pressure-controlled cycles that utilize an inverse ratio ventilation strategy and spontaneous breaths. The two valves of the ventilator are continuously open thereby enabling spontaneous breaths during any phase of the respiratory cycle. APRV can also be used with very short time at low pressure. Studies in ARDS, using APRV with unsupported spontaneous breaths ([Putensen et al. 1999](#); [Putensen et al. 2001](#); [Putensen et al. 2006](#)) have revealed that maintaining endogenous breathing may improve pulmonary function via lung recruiting ([Putensen et al. 1999](#)), and may shorten the duration of mechanical ventilation as a result of reduced requirements for sedation ([Putensen et al. 2001](#)). A trial assessing the utility of APRV in ARDS is ongoing. This study mandates a 24-hour period of full sedation and neuromuscular blockade at inclusion which is consistent with current evidence for the beneficial effects of early use of neuromuscular blocking drugs previously noted ([Papazian et al. 2010](#)) and the current recommendations for management of the most severely hypoxemic ARDS patients ([Ferguson et al. 2012](#)).

Pressure support ventilation (PSV) is often used during the weaning period. It is increasingly being used at an early stage in the disease process whilst patients require significant support with regards FiO<sub>2</sub> (up to 0.6) and PEEP (8-10 cm H<sub>2</sub>O) ([Xirouchaki et al. 2008](#)). It is mandatory to monitor the VTs to maintain protective ventilation (see below). The optimal time to transition from assisted controlled ventilation to PSV is unknown but should be considered when the majority of the ventilator cycles are triggered by the patient and when the underlying disease is being under control. When this occurs the back-up rate should be reduced to promote assisted cycles. Another promising mode of support for spontaneous breathing is the neurally adjusted ventilatory assisted mode (NAVA) which reduces patient-ventilator dyssynchrony by triggering assisted breaths via a diaphragmatic EMG placed in a specialized naso-gastric catheter ([Sinderby et al. 1999](#)).



#### Notes

- Complete inactivity of the diaphragm may rapidly induce marked muscle atrophy
- APRV allowing spontaneous breathing may shorten duration of mechanical ventilation
- A strategy of ventilation using controlled ventilation without spontaneous breathing is currently recommended in the most hypoxemic ARDS patients



#### References

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## 6. 2. VILI during spontaneous breathing

Whereas strict control of low  $V_T$  is the general rule in ARDS, the negative pleural pressures generated during spontaneous breathing whilst being mechanically ventilated can increase  $V_T$  and transpulmonary pressure (Slutsky and Ranieri. 2013; Akoumianaki et al. 2014) . In an experimental model of ARDS high transpulmonary pressures generated by huge spontaneous breaths worsened lung injury. On the one hand spontaneous breathing can improve lung recruitment in cases of mild ARDS but on the other it can lead to worsening lung injury in severe ARDS (Yoshida et al. 2013).

### Notes

- Spontaneous breathing may promote VILI, especially in the most severe ARDS patients



## References

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### 6. 3. Patient ventilator dyssynchronies

The most common dys-synchrony observed is known as double-triggering which is most likely to occur in hypoxemic patients ventilated by VCV with a short insufflation time (Thille et al. 2006; Nin et al. 2017). In double-triggering the patient's supported breath is incomplete and continues beyond the end of the first ventilator cycle triggering a second ventilator insufflation, effectively meaning that there is a twofold increase in the  $V_T$  (Putensen et al. 2001). It is detected as two consecutive ventilator cycles separated by either a short or absent expiratory period. Use of low  $V_T$  and high flow rates can lead to short insufflation times which places the patient at risk of double-triggering if their effort continues beyond the ventilator insufflation time. The primary concern with double-triggering is the risk of deleterious high  $V_T$ s. Options available to avoid this include increasing sedation and the addition of neuromuscular blockers. If gas exchange is improving the mode can be switched from assisted-controlled ventilation to PSV (Chanques et al. 2013). However, if the  $V_T$  generated in PSV becomes excessive, it may be necessary to return to the assisted controlled ventilation to minimize VILI. In this situation, assisted controlled ventilation should be set with a longer inspiratory time, either by switching from a constant to a decelerating flow, or by reducing peak flow and/or adding a pause (Nin et al. 2017).

Another mechanism of double-triggering known as "reverse triggering" has been described in patients heavily sedated and ventilated by VCV or PCV (Akoumianaki et al. 2013). Reverse-triggering occurs when a ventilator-controlled cycle is followed by a second patient-triggered cycle, as if the ventilator-controlled cycle triggered a spontaneous patient breath. With an esophageal balloon in place reverse triggering was found to be associated with a drop in esophageal pressure occurring after the mechanical breath (Muriel et al. 2015). This form of reverse triggering should be avoided in the same manner as previously described. It should be mentioned that reverse triggering can be followed by a double triggering and, under those conditions the strategy should be to wait for the patient to take control of breathing. Further studies are ongoing to determine the prevalence, risk factors and impact of reverse triggering.



## Notes

- The main dys-synchrony in ARDS is double-triggering
- Double-triggering generates a  $V_t$  that is too large
- Double triggering can result from reverse triggering without any effort from the patient.



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## 7. Monitoring During Mechanical Ventilation in ARDS

### 7. 1. Respiratory mechanics

Assessment of respiratory mechanics remains of primary importance in the management of mechanically ventilated patients with ARDS. This section will focus on the respiratory mechanics assessed during passive mechanical ventilation.

#### Airway pressure

Peak pressure is monitored on every ICU ventilator. However, it includes resistive and elastic components and is also dependent on the inspiratory flow rate. In VCV end-inspiratory occlusion can separate resistive (peak pressure minus plateau pressure) and elastic (plateau pressure) components of the total (peak) pressure. By dividing the resistive pressure by the flow immediately preceding occlusion, respiratory resistance can be obtained.

#### Plateau pressure

Plateau pressure is the common term used to define the elastic component of the total pressure dissipated into the respiratory system after VT delivery. It is measured from the airway pressure tracing and reflects the alveolar pressure. If the esophageal pressure is measured the trans-pulmonary plateau pressure can be obtained (see below). Plateau pressure must be determined at zero flow (static condition), a situation that can be achieved by either accommodating a short period of zero flow within the inspiratory time or by occluding the airways by manually pressing a specific button on the ventilator (see above). Having done that, plateau pressure can be recorded at different time points (Figure 3): immediately after airway occlusion at the first zero flow, 0.5 sec or 3 sec after airway occlusion onset. In the lower VT arm of the ARMA trial ([Acute Respiratory Distress Syndrome et al. 2000](#)), which was associated with better survival, plateau pressure was recorded 0.5 sec after airway occlusion and had to be maintained equal to or below 30 cmH<sub>2</sub>O. More recently, physiologic studies suggested that the safety threshold should be set even lower at less than 27 cm H<sub>2</sub>O ([Terragni et al. 2007](#)). It is worth noting that in the LUNG SAFE study only 40% of patients had their plateau pressure measured ([Bellani et al. 2016](#)).



Figure 2: Airway or trans-pulmonary pressure (P) over time during volume controlled mode at constant flow inflation (not shown).

**Figure 2:** Airway or trans-pulmonary pressure (P) over time during volume controlled mode at constant flow inflation (not shown). During the period of inspiration limited within the double vertical dotted lines the equation  $P = a \times \text{time}^b + c$  is fitted. The exponent b is the stress index. In

the middle panel  $b = 1$  indicating constant elastance during insufflation and hence homogeneous expansion of the lung overall. In the left panel,  $b < 1$  indicating reduced elastance (increased compliance) over the inflation and, hence risk of recruitment/derecruitment (atelectrauma). In the right panel  $b > 1$  indicating increased elastance (reduced compliance) over inflation, and hence risk of overinflation (volutrauma). For further explanations see text.

### Trans-pulmonary pressure

Trans-pulmonary pressure reflects the overall stress imposed on the lung. It is measured at the end of both expiration and inspiration in static conditions (zero flow). At the end of expiration it is measured by subtracting PEEP from the absolute oesophageal pressure at end expiration (Figure 2). At the end of inspiration, trans-pulmonary pressure is computed in two ways: by subtracting oesophageal pressure from airway plateau pressure or by calculating the product of airway plateau pressure and the ratio of lung to total respiratory system elastance (the inverse of compliance). This ratio, which is 0.5 in normal subjects, can vary between 0.2 and 0.8 in ARDS patients (Chiumello et al. 2008). This explains why a plateau pressure of 30 cmH<sub>2</sub>O may be associated with a trans-pulmonary plateau pressure ranging from 10 to 25 cmH<sub>2</sub>O depending on the patient (Chiumello et al. 2008).

The upper safety level of trans-pulmonary pressure has not been established yet, but should be below 25 cmH<sub>2</sub>O. Trans-pulmonary pressure measured at the end of expiration has been suggested to be maintained above 0 cmH<sub>2</sub>O as an opening pressure threshold (Talmor et al. 2008). A large clinical trial is ongoing to demonstrate whether or not maintaining end-expiratory trans-pulmonary pressure measured at zero flow (i.e. total trans-pulmonary end-expiratory pressure) in the 0-6 cm H<sub>2</sub>O range improves survival (Fish et al. 2014). If this were to be the case management of patients with ARDS would be changed significantly. Whatever the results, oesophageal pressure monitoring provides a useful additional tool when monitoring ventilator strategies.

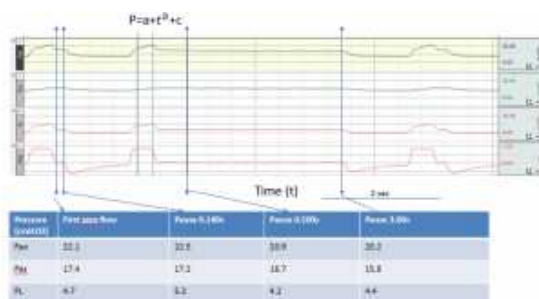


Figure 3: From top to bottom airway ( $P_{ao}$ ), esophageal ( $P_{es}$ ), transpulmonary (PL) pressures and flow over time (t) during volume controlled mode at constant flow insufflation.

**Figure 3:** From top to bottom airway ( $P_{ao}$ ), esophageal ( $P_{es}$ ), transpulmonary (PL) pressures and flow over time (t) during volume controlled mode at constant flow insufflation. The first and third breath accommodate a short inspiratory pause. The second breath includes a manual prolonged end-inspiratory occlusion. The four double arrowed vertical lines show the different time to measure elastic pressures at zero flow, whose values are provided in the table. The two dotted vertical lines isolate the period of zero flow to which the equation (top) is fitted to obtain the stress index (constant  $b$ ). For further explanations see text.

### Driving pressure

The driving pressure is the difference in alveolar pressure between end-expiration and end-inspiration, or the difference between PEEP<sub>tot</sub> and plateau pressure (Figure 2). The same also applies for the lung if trans-pulmonary pressure is taken into account. This pressure results from

the delivery of VT in volume controlled mechanical ventilation and determines the VT in pressure controlled mechanical ventilation. Therefore, it indirectly reflects lung strain. A post-hoc analysis of clinical trials comparing ventilation strategies in ARDS suggested that driving pressure was the strongest (ventilatory parameter) predictor of hospital mortality (Amato et al. 2015). There was a significant positive relationship between adjusted hospital mortality and driving pressure with a threshold in the vicinity of 15 cm H<sub>2</sub>O driving pressure (Amato et al. 2015). Finally, driving pressure could be the mediator by which either PEEP or plateau pressure has an impact on mortality (Amato et al. 2015). However, whether or not controlling for a specific value of driving pressure would improve outcomes is unknown. One caveat to the above study (Amato et al. 2015) is that driving pressure was calculated from measurements made at different time points across studies and hence the evidence may depart from the accurate measurements defined above.

Compliance. Compliance is the ratio of VT to driving pressure and reflects the mass of alveoli open throughout the respiratory cycle. It can be considered as an indicator of the volume of aerated lung otherwise known as “baby lung” (Gattinoni and Pesenti. 2005) and as such reflects the severity of ARDS. Assuming 100 ml/cmH<sub>2</sub>O is reflective of normal compliance, a value of 40 ml/cmH<sub>2</sub>O approximates to a loss of 60% of aerated lung volume.

Stress index During insufflation at constant flow the increase in airway (or trans-pulmonary) pressure has been modelled as a function of time, which is equivalent to volume (V) , as follows:

$$Pressure = a * V^b + c$$

where **a** is elastance at **V** = 1 liter, **b** the shape of change in pressure as a function of volume and **c** the intercept. With **b** (stress index) equal to, greater or lower than 1, the elastance is constant, increases (overdistension) or decreases during insufflation (Figure 3). Settings targeting stress index to 1 should be an attractive mechanical ventilation strategy. However, even though it has been shown that stress index maintained close to 1 is associated with less lung inflammation (Terragni et al. 2013), no data yet show improved patient outcome.

#### Notes

- monitoring of respiratory mechanics under passive mechanical ventilation in ARDS is essential and easy to do in sedated and paralyzed subjects.
- the primary variable to monitor is plateau pressure
- assessment of trans-pulmonary pressure is possible with the use of an oesophageal pressure monitor

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## 7. 2. Gas exchange (alveolar dead space)

Measurement of exhaled CO<sub>2</sub> concentration is easy and should be performed in all ventilated patients.

Physiologic dead space is given by (Bellani et al. 2016):

$$V_{Dphysiol} = V_{Dalv} + V_{Danat} + V_{Dapparatus}$$

where  $V_{Dalv}$  is alveolar dead space,  $V_{Danat}$  anatomical dead space due to airway and  $V_{Dapparatus}$  anatomical dead due to any apparatus located between mouth/tip of the endotracheal tube and the Y piece of the ventilator circuit or leak in invasive or non-invasive mechanical ventilation systems respectively.

Volumetric exhaled CO<sub>2</sub> measurement which is available in some ICU ventilators can provide end-tidal CO<sub>2</sub>,  $V_{Danat}$  and an estimate of  $V_{Dalv}$  with the use of arterial blood gases it is possible to calculate  $V_{Dphysiol}$ .

The Bohr dead space is calculated as:

$$\frac{V_D}{V_T} Bohr = \frac{P_{ETCO_2} - P_{ECO_2}}{P_{ETCO_2} * V_T}$$

where  $P_{ETCO_2}$  is end-tidal PCO<sub>2</sub> and  $P_{ECO_2}$  mixed expired PCO<sub>2</sub>. Enghoff modified this equation by replacing end-tidal PCO<sub>2</sub> with PaCO<sub>2</sub> (Richard et al. 2003; ARDS Definition Task et al. 2012). Note that the "Enghoff" dead space is increased in conditions which increase



pulmonary shunt. Dead space measurement is useful for assessing prognosis and for evaluating the effect of prone positioning as well as PEEP titration.

Thus, a high Enghoff VD/VT (as a sign of severe lung collapse/consolidation) in ARDS is associated with poor prognosis, and a reduced VD/VT by prone position (reducing shunt by recruitment of previously collapsed lung units) indicates a good prognosis.

Furthermore, it is a good compliment to lung mechanics to detect changes in ventilation, e.g., due to disconnection, leakage, secretions, lung collapse or pneumothorax and, in addition, gives an early warning of circulatory failure by showing a reduced CO<sub>2</sub> elimination or reduced end-tidal CO<sub>2</sub> concentration (e.g. in cases of pulmonary emboli, shock or cardiac arrest for example).

#### Notes

- Exhaled CO<sub>2</sub> is important for estimation of dead space ventilation and changes in ventilation and perfusion.

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## 7. 3. Lung volumes

End-expiratory lung volume (EELV) is a basic lung functional measurement as it is the amount of aerated lung at the end of expiration and hence is the absolute lung volume most commonly monitored at the bedside. EELV can be used to evaluate for collapse or overdistension and to set or assess the effect of PEEP. Low values of EELV have consistently been found in patients with ARDS which characterises it as a restrictive lung disease. This finding was one of the basic tenets of the concept of the “baby-lung” ([Gattinoni and Pesenti. 2005](#); [Gattinoni et al. 2016](#)) . The only suitable bedside techniques which allow measurement of EELV are the gas dilution methods. The amount and concentration of a tracer gas (usually Nitrogen or Helium) measured in the lungs allows for calculation, The multiple breath Nitrogen wash in/washout technique has been integrated into one ventilator brand ([Chiumello et al. 2008](#)) . There are several problems with assessing EELV at the bedside however. EELV is underestimated with these methods in patients with long regional time constants (resistance x compliance) as seen with for example chronic obstructive lung disease; or large EELVs (high PEEP) particularly when low VTs are used

during the measurements. Furthermore, a high EELV does not indicate whether the lung is healthy overdistracted or whether previously collapsed lung regions have been recruited. Moreover, circuit leak can compromise measurements. These limitations should be considered when EELV measurements are used to fine tune ventilator settings in patients with ARDS.

#### Notes

- Lung volume measurements can easily be performed at the bedside but the results need to be carefully interpreted

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## 7. 4. Lung imaging

The clinical usefulness of chest radiography and CT has previously been described in the module.

**Lung ultrasound** is a bedside method of imaging developed extensively over recent years ([Lichtenstein et al. 2004](#); [Lichtenstein et al. 1997](#)). Indeed the use of lung ultrasound is becoming a core skill. With a standardised approach it is possible to diagnose the presence of pleural fluid, pneumothorax, alveolar interstitial fluid and consolidation. It may also be used to evaluate PEEP settings and recruitment though it cannot assess for overdistension of lung units. Further advantages include the fact that it is considered more diagnostically reliable than chest radiography in ARDS; it is always available; measurements can be repeated quickly and an assessment of cardiac function can be made. Figure 5 shows a collapsed lung at this end of expiration, which becomes re-created after a recruitment manoeuvre.

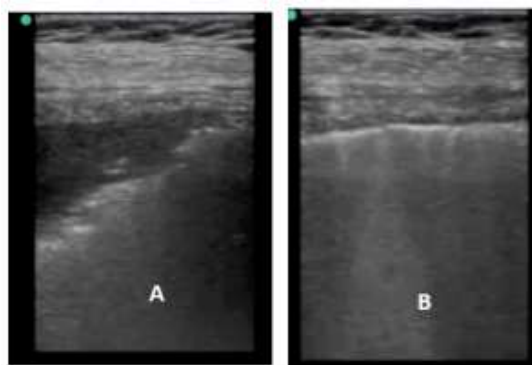


Figure 5: Courtesy by Dr Gerardo Tusman and Celicia Acosta, Hospital Privado de Comunidad, Mar del Plata, Buenos Aires, Argentina

**Figure 5:**

Ultrasound images at end-expiration before (A) with lung collapse and air bronchograms and after lung recruitment (B), where the lung parenchyma is normalized.

**Electric impedance tomography (EIT)** uses electric currents in order to image the air content of the lungs (Frerichs et al. 2017). It is a continuous method of imaging in which 16 to 32 electrodes are either placed separately or on a belt around the circumference of the lower thorax. These electrodes are both transmitters and receptors of small electric currents. Since air has a higher impedance than tissue and body fluids EIT allows evaluation of changes in aeration within the thorax during ventilation. Current methods can obtain 50 images per second. It is possible to evaluate regional differences in ventilation patterns and whether lung units have collapsed or whether a recruitment maneuver has been successful. In addition, it may be useful when optimising PEEP for the reasons outlined (Figure 6). By injecting hypertonic saline (which has a low impedance) via a central catheter it is possible to evaluate regional pulmonary perfusion, as shown in figure 6. The drawbacks of EIT include the fact that it does not assess aeration only changes in aeration during ventilation and it only covers a 2-3 cm frontal- dorsal slice of the lungs. Videos (figures 7 and 8) obtained by Enlight 18000 from Timpel Medica provides dynamic images of the figure 6 for ventilation and perfusion, respectively. Videos are from the courtesy by Dr. Fernando Suarez Sipmann, Hedenstierna Laboratory, Uppsala University, Sweden and CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. Videos (figures 7 and 8). On the videos note the delay in perfusion to the right lung.

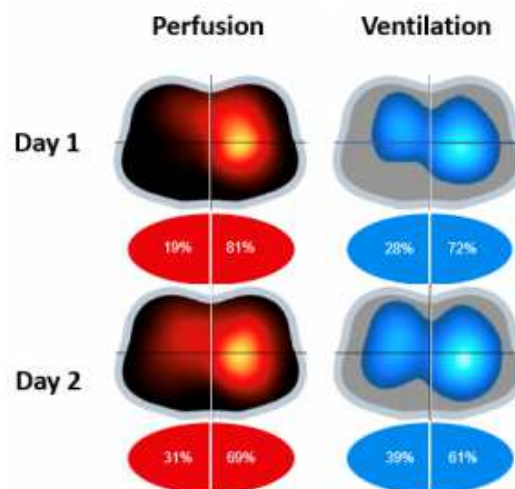


Figure 6: EIT images showing perfusion. Courtesy by Dr. Fernando Suarez Sipmann, Hedenstierna Laboratory, Uppsala University, Sweden and CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.

**Figure 6:**

EIT images showing perfusion (by injection of 10 ml 7% NaCl in a central line) and ventilation of the lungs in an elderly women with ARDS due to pneumococcal pneumonia that mainly affected the right lung. The numbers below the images indicate the percentage of the total perfusion and ventilation, respectively, to the right and left lungs. Note the improvements in both perfusion and ventilation after optimization of ventilation from day 1 to day 2, also reflected in improved Crs from 29 to 44 ml/cmH<sub>2</sub>O. The images were obtained by Enlight 18000 from Timpel Medica. Courtesy by Dr. Fernando Suarez Sipmann, Hedenstierna Laboratory, Uppsala University, Sweden and CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.

- Lung ultrasound is an important tool for detection, monitoring and treatment of lung and pleural pathologies in ARDS.
- It is yet unclear whether EIT will influence the management of ARDS.

### Figure 7: Regional Ventilation Movie



## Regional Ventilation Movie

from **ESICM Channel**



### Figure 8: Perfusion Wave front Movie



# Perfusion Wave front Movie

from [ESICM Channel](#)

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## 8. Complications

The main complications encountered when managing patients with ARDS are barotrauma, hemodynamic impairment, acute cor pulmonale and ventilator-associated pneumonia.

### 8. 1. Barotrauma

The high stresses generated during mechanical ventilation can cause barotrauma leading to bronchial or alveolar rupture which is evidenced by air leak detected on chest X-ray (Figure 4) as pneumothorax or pneumomediastinum. Barotrauma can cause air to leak into: the mediastinum; the pleura causing pneumothorax; the subcutaneous tissues leading to surgical emphysema; the retroperitoneum or the oesophagus.. The incidence of pneumothorax in patients ventilated with ARDS was as high as 40% prior to the era of protective mechanical ventilation ([Gammon, Shin and Buchalter. 1992](#); [Gammon et al. 1995](#)). As VT and plateau pressures have been reduced the incidence of pneumothorax has also reduced to between 5 and 10% ([Meade et al. 2008](#); [Mercat et al. 2008](#); [Brower et al. 2004](#); [Guérin, Reignier and Richard. 2013](#); [Papazian et al. 2010](#)). It is important to note that the incidence of pneumothorax did not differ with low or high levels of PEEP ([Meade et al. 2008](#); [Mercat et al. 2008](#); [Brower et al. 2004](#)). Rates of pneumothorax and barotrauma increase markedly when plateau pressures above exceed 35 cmH<sub>2</sub>O regardless of level of PEEP ([Amato et al. 1998](#); [Boussarsar et al. 2002](#)).

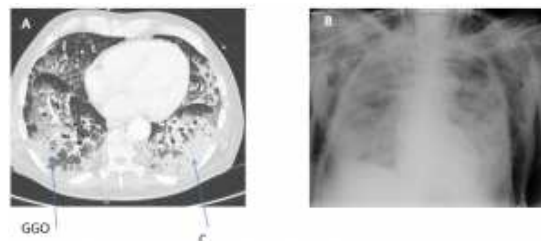


Figure 4: A. Lung CT scan of an ARDS patient with H1N1 ARDS at day 1 after tracheal intubation showing ground glass opacities (GGO) and consolidation (C). B. Chest X ray of the same patient done 6 days later showing bilateral opacities and bilateral subcutaneous emphysema without obvious pneumothorax. This patient could have an anterior pneumothorax, but this can only be visualized by CT or ultrasonography. Plateau pressure was 28 cmH<sub>2</sub>O.

Pneumothorax leads to an increase in plateau pressure during VCV (as a result of reduced lung compliance) or a decrease in VT during PCV. Ultimately, oxygenation is impaired. If hypoxia is profound cardiac arrest may ensue. Signs of pneumothorax include subcutaneous emphysema and unilateral absence of breath sounds which can be confirmed by immediate lung ultrasound examination ([Lichtenstein et al. 1999](#); [Lichtenstein et al. 2000](#); [Lichtenstein et al. 2005](#)). Occasionally, a CT scan is necessary to diagnose an occult pneumothorax. If the patient has signs of a tension pneumothorax, needle aspiration or chest tube drainage should be performed

immediately. The site for needle aspiration is the second intercostal space in the mid-clavicular line of the hemithorax whereas a chest tube is usually inserted into the fifth intercostal space (nipple level), anterior to the midaxillary line.

In the large RCT performed by the ARDS network group comparing low versus high VT the plateau pressure was maintained below 35 cmH<sub>2</sub>O in both groups. This led to a 10% incidence of pneumothorax in both groups ([Acute Respiratory Distress Syndrome et al. 2000](#)). However, the mortality was significantly lower in the lower VT group suggesting that VILI was microscopic. This microscopic barotrauma, leading to biotrauma, is common and it has been hypothesised that this kind of injury could be an important contributor to multiple organ dysfunction and mortality ([Slutsky and Tremblay. 1998](#); [Ranieri et al. 1999](#); [Imai et al. 2003](#)). In the Acurasys trial, the rate of pneumothorax was significantly lower in the neuromuscular blocking agent group than in the placebo group suggesting that the lower mortality in the former may result from less VILI. Since plateau pressure was the same in both groups, VILI in the placebo group may have resulted from either higher regional stress (high regional transpulmonary pressure) and/or a higher rate of dys-synchronies. It should be noted that dys-synchronies may also occur under paralysis.

#### Notes

- Nowadays, the incidence of pneumothorax is below 10% in ARDS
- The risk of barotrauma does not depend on PEEP level but increases when plateau pressure exceeds 35 cm H<sub>2</sub>O
- Lung ultrasound may help to diagnose pneumothorax

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## 8. 2. Hemodynamic impairment

Hemodynamic impairment is frequent in ARDS. Indeed, almost 3 patients of 4 require vasopressors at inclusion to RCTs in ARDS (Mercat et al. 2008; Guérin, Reignier and Richard. 2013). This is not surprising as sepsis is the primary cause of ARDS and septic shock promotes vasoplegia or a low cardiac output. Shock may also be a direct consequence of mechanical ventilation. Because mechanical ventilation generates positive pressures within the thorax, venous return is impeded; right ventricular ejection is further impaired by compression of alveolar capillaries. This ultimately leads to a reduction in cardiac output (Fougères et al. 2010). The mean airway pressure is probably more important than either the PEEP level or peak airway pressure. The intermittent decrease in venous filling caused by the positive intrathoracic pressure produces a variation in systemic arterial pressure (systolic pressure or pulse pressure variation).

### Notes

- Around 75% of the patients need vasopressors at the early stage of ARDS





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### 8. 3. Acute cor pulmonale

Acute cor pulmonale results from increased right ventricular afterload. This is a frequent complication of ARDS and is due to, amongst other things, hypoxemic pulmonary vasoconstriction and compression of pulmonary capillaries by positive pressures leading to increased pulmonary vascular resistance and impaired right ventricular ejection. A rise in right ventricle afterload leads to dilation of the right ventricle and subsequently septal dyskinesia which can be detected by echocardiography (Vieillard-Baron et al. 2002). Acute cor pulmonale is considered as severe when the right ventricle becomes larger than the left ventricle. The incidence of acute cor pulmonale during ARDS is around 20% overall and 10% in its severe form (Boissier et al. 2013; Mekontso Dessap et al. 2016). The occurrence of severe acute cor pulmonale is independently associated with increased mortality (Mekontso Dessap et al. 2016). In these conditions, echocardiography should be systematically performed in patients with ARDS and shock in order to assess left ventricular function but also to detect acute cor pulmonale. Management of right ventricle failure aims at lowering right ventricle afterload and increasing its contractility. Pharmacological interventions to achieve these goals are iNO, dobutamine and diuretics. Prone position by improving gas exchange and recruiting the lung allows lower PEEP and can treat right ventricle failure (Vieillard-Baron et al. 2007).



## Notes

- Acute cor pulmonale is diagnosed on echocardiography by the presence of a dilated right ventricle and septal dyskinesia
- Acute cor pulmonale occurs in almost 20% of cases of ARDS, and almost 10% in its severe form
- Severe acute cor pulmonale is independently associated with increased mortality in ARDS



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## 8. 4. Ventilator associated pneumonia

Patients with ARDS are more likely to develop ventilator-associated pneumonia (VAP) due to prolonged duration of invasive mechanical ventilation through an endotracheal tube (Chastre et al. 1998). VAP is associated with an increased length of stay and perhaps an additional mortality. Bacteriological samples should be systematically taken in cases of fever, an inflammatory syndrome, an increase in sputum production, new infiltrates on the chest radiograph or deterioration in oxygenation. However, diagnosis of VAP is particularly difficult in patients with ARDS as they frequently exhibit evidence of an inflammatory response, have diffuse infiltrates on chest x-ray and worsening of oxygenation occurs for multiple reasons. For this reason, systematic quantitative cultures of tracheal aspirates two or three times a week should be considered to allow early detection of pulmonary infection and thus early initiation of adequate antibiotic therapy (Delclaux et al. 1997).



### Notes

- The diagnosis of VAP is difficult in ARDS and systematic quantitative cultures may help in early detection



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## 8. 5. Persistent (or non resolving) ARDS

Persistent or non-resolving ARDS is present when criteria remain after 5-7 days. Once VAP and fluid overload are excluded lung histological examination by open lung biopsy might be

considered. Several centres have reported their experience in performing biopsy with low complication rates (Guerin et al. 2015; Papazian et al. 2007; Kao et al. 2006; Lim et al. 2007). In 2007, a case series of 100 patients with ARDS suggested that open lung biopsy provided evidence of cytomegalovirus pneumonia which led to the administration of antiviral agents (Papazian et al. 2007). A few years later however, the same investigators, found that the use of rapid virology diagnostic tests allowed the detection of active cytomegalovirus infection without performing this invasive procedure (Coisel et al. 2012). More recently, it has become apparent that a high proportion of patients with ARDS-like symptoms have organizing pneumonia (Guerin et al. 2015) which could potentially be responsive to steroids. This condition could correctly be diagnosed by high-resolution CT chest however which is a much less invasive approach than open lung biopsy. Biopsy would also allow for the accurate identification of fibrosis though the administration of steroids is not recommended at this stage of ARDS (Steinberg et al. 2006). For these reasons a complete investigation of ARDS should include polymerase chain reaction, immunologic assay, bronchoalveolar lavage and lung CT. This should enable early identification of almost all differential diagnoses meaning open lung biopsy should only be necessary in exceptional cases. In the LUNG SAFE study (Bellani et al. 2016), very few patients were investigated with bronchoalveolar lavage. Best practice would suggest this investigation should be in any work-up since the objective should always be to identify the underlying cause of ARDS.

#### Notes

- Persistent or non-resolving ARDS is diagnosed as ARDS lasting at least 5 to 7 days
- Complete investigation by including broncho-alveolar lavage and lung CT should enable early identification of almost all diagnosis associated with or mimicking ARDS
- Open lung biopsy should only be performed in rare instances.

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## 9. Outcomes

### 9. 1. Mortality according to the aetiology of ARDS and causes of death

Patients developing ARDS as a result of trauma have better survival rates than for other causes of ARDS (Eisner MD et al. 2001). There is no difference in mortality between patients developing ARDS as a result of pulmonary disease as compared to those with an extrapulmonary origin (Eisner et al. 2001). Recently, 2 sub phenotypes of ARDS were identified (Calfee et al. 2014). The hyper inflammatory sub phenotype was characterized by more severe inflammation and a higher prevalence of sepsis. These patients were more likely to have shock and metabolic acidosis, and they had higher mortality rates.

The main cause of death for patients with ARDS is sepsis complicated by multi-organ failure; the rates of death due to refractory hypoxemia do not exceed 20% of cases (Thille et al. 2013; Montgomery et al. 1985; Stapleton et al. 2005). Death as a result of withdrawal of life support measures has increased over time (Stapleton et al. 2005), and the vast majority of deaths amongst patients with ARDS were preceded by a "do not resuscitate" order (Mehter, Wiener and Walkey. 2014).



#### Notes

- The mortality of patients with ARDS of pulmonary origin is similar to that of patients with ARDS of extrapulmonary origin



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## 9. 2. Change in outcomes over time

Since the turn of the century several studies have demonstrated that lung protective ventilation leads to improved survival ([Amato et al. 1998](#); [Acute Respiratory Distress Syndrome et al. 2000](#); [Briel et al. 2010](#)). After 2010, two large RCTs demonstrated a reduction in mortality associated with the use of neuromuscular blockers ([Papazian et al. 2010](#)) and prone positioning ([Guérin et al. 2013](#)). Despite this, overall mortality has not changed substantially during the last decade, and remains greater than 40% for patients with moderate or severe ARDS in observational studies ([Villar, Blanco and Kacmarek. 2016](#)).

The positive results reported in RCTs may not accurately reflect the situation in non-selected patients with ARDS within ICU: mortality for ARDS was lower in RCTs than in observational studies that are closer to real life ([Phua et al. 2009](#)). Indeed, patients included in RCTs are expressly selected and those with major comorbidities such as hematological malignancies, cirrhosis, and chronic cardiac or respiratory disease are usually excluded. Moreover, a high proportion of patients potentially eligible are not enrolled. The outcome of ARDS patients enrolled in a recent RCT has been compared to that of patients who met inclusion criteria but who were not enrolled in the study due to various reasons ([Arabi et al. 2015](#)). The patients who were included in the study had lower mortality than those who were potentially eligible but not enrolled, suggesting that enrollment in clinical trials may be associated with improved outcomes. The better outcomes reported for patients included in RCTs may be a result of the “Hawthorne” effect or as a consequence of optimal management including standardised lung protective ventilation and application of other effective therapies. Observation of actual management as occurred in the recent LUNG SAFE study revealed that 35% of patients with ARDS were ventilated with a VT above 8 ml/kg of PBW; the mean PEEP level was  $8 \pm 3$  cm H<sub>2</sub>O in moderate and  $10 \pm 4$  cm H<sub>2</sub>O in severe ARDS and prone positioning was used in only 16% of the patients with severe ARDS. Therefore, in 2014, patients with ARDS were receiving excessively high VT and excessively low levels of PEEP in “real life” while plateau pressure was measured in only 40% of cases.



### Notes

- Mortality in ARDS is lower in RCTs than in observational studies
- In real life, measures that have shown beneficial effects are not routinely applied and enrollment in clinical trials is associated with improved outcomes



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### 9. 3. Long term outcome

Fibrosis is rare within the first week of ARDS, however, it can be observed as early as the second week and its prevalence markedly increases beyond the third week of the onset of ARDS, especially in ARDS of pulmonary origin (Thille et al. 2013). Patients with fibrosis have altered lung compliance and more frequently demonstrate interstitial opacities on chest x-ray (Matamis et al. 1984). Following recovery, patients with fibrosis may have more long-term residual pulmonary dysfunction than patients without (Burnham et al. 2014). Six months after hospital discharge patients still had radiological reticulations on chest CT scan; and altered total lung capacity, forced vital capacity and carbon monoxide diffusion capacity (Burnham et al. 2013). Limitation in exercise is due to both pulmonary impairment and neuromuscular weakness. Herridge and colleagues followed ARDS survivors discharged from hospital for 5 years (Herridge et al. 2003; Herridge et al. 2011). Although patients had normal lung volumes and spirometry measurements by 6 months, carbon monoxide diffusion capacity remained low and six-minute-walk test was markedly altered (Herridge et al. 2003). At five years, patients did not return to normal predicted levels of physical function with persistent exercise limitation and decreased physical quality of life (Herridge et al. 2011). The median 6-minute walk distance was 281m at 3 months, 422m at 1 year and 436m at 5 years, which are only 76% of predicted distance. Health-related quality of life was mainly altered as a result of extrapulmonary complications: muscle weakness and fatigue were the main reasons for functional limitation (Herridge et al. 2003; Herridge et al. 2011; Fan et al. 2014). Moreover, 1 or 2 years after ARDS, the majority of survivors present with clinically significant general anxiety, depression, and posttraumatic stress disorder symptoms (Bienvenu et al. 2015), and even sometimes psychiatric symptoms (Huang et al. 2016).

## Notes

- Lung volumes and spirometry measurements return to normal values within months
- The median 6-minute walk distance remains markedly altered with persistent exercise limitation and decreased physical quality of life several years after surviving ARDS
- Muscle wasting, weakness and fatigue are the main long-term complications in ARDS

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