# Chapter 6
# Acute Respiratory Distress Syndrome


**Yu-Mei Wang and Guang-Qiang Chen**

Acute respiratory distress syndrome (ARDS) can be caused by several diseases. The symptoms are characterized as impaired gas exchange, decreased lung compliance, increased lung weight, and widespread involvement of the lung parenchyma. No matter what causes ARDS, the treatment of symptoms is mandatory to save time for the resolution of the underlying process [1]. ARDS patients need mechanical ventilation [2]. The mortality of mechanically ventilated patients remains as high as 30–40% [3]. Despite being life-saving, mechanical ventilation also can be harmful for the lungs as well as the diaphragm [4]. During mechanical ventilation, especially passive ventilation, inappropriate ventilator settings can worsen lung injury, which is called ventilation-induced lung injury (VILI). In the transition to assisted ventilation, harmful patient–ventilator interactions might occur. Understanding the physiology of ARDS and better respiratory monitoring will help clinicians adapt the best available evidence with the ultimate goal of improving morbidity and mortality. This chapter summarizes respiratory monitoring in ARDS to provide more protective ventilation. Most of the physiological concepts are mentioned above.

## 6.1 Physiology of ARDS

The concept of ARDS was born more than 50 years ago. Ashbaugh and colleagues reported 12 cases of young patients with severe acute respiratory failure with bilateral pulmonary infiltrates, decreased compliance, poor oxygenation refractory to supplemental oxygen, and in some cases impaired carbon dioxide clearance [5].

The current Berlin definition characterizes ARDS by bilateral lung infiltrates on chest imaging due to pulmonary edema [2]. Three main physiological consequences

Y.-M. Wang · G.-Q. Chen (✉)
Department of Critical Care Medicine, Beijing Tiantan Hospital, Capital Medical University, Beijing, China



J. Zhou et al. (eds.), *Respiratory Monitoring in Mechanical Ventilation*,
https://doi.org/10.1007/978-981-15-9770-1_6

are included in ARDS: a defect in oxygenation, a high dead space, and a dramatic reduction in lung volumes as illustrated by a functional residual capacity of around 40% predicted and this reduction is inhomogeneous [6]. In addition, the study of chest computed tomography (CT) reported that the lung was heterogeneous and a small amount of air remained in aerated areas [7]. This led to the popular concept of "baby lung" proposed by Gattinoni and Pesenti, which refers to the small amount of normally aerated lung units [8]. The first CT scan images obtained in ARDS patients, show that densities were preferentially distributed in the dependent lung regions, but relatively less in the independent lung area. This view is in contrast to the commonly accepted lung heterogeneity in ARDS patients. CRS has decreased accordingly not because of stiffer lungs, but due to a small number of aerated lung units with normal compliance. Therefore, with mechanical ventilation, the insufficiency of a given VT in a small aerated lung will generate higher pressures in ARDS than in normal lungs.

These characteristics may have clinical consequences, which is defined as VILI, (1) barotrauma (alveolar air leaks such as pneumothorax, pneumomediastinum, or subcutaneous emphysema) [9]; (2) volutrauma (overdistension of aerated lung regions) [10]; (3) atelectrauma (repeated opening and closing of some lung regions) [11]; (4) decreased cardiac output by means of a decrease in the left ventricular preload [12]; and an increase in right ventricular afterload up [13]. All these consequences are harmful to the patients.

Imbalance of lung ventilation and perfusion is also an important characteristic of ARDS [14]. Because of lung heterogeneity, some lung regions are better ventilated than perfused (such as dead space), whereas others are less ventilated than perfused or nonventilated at all (i.e., intrapulmonary shunt) [15]. Dead space is related to lung microcirculatory occlusion, to a certain extent to shunt and potentially to distension, and is an independent predictor of mortality in ARDS [16]. Impaired $CO_2$ clearance is the main clinical consequence of dead space and it can be corrected by increasing alveolar ventilation. And the main clinical consequence of intrapulmonary shunt is hypoxemia without significant improvement by an increase of $FiO_2$ [15].

## 6.2 Monitoring Gas Exchange

In general, $FiO_2$ can be monitored by the ventilator to ensure that sufficient concentration of $O_2$ is delivered to the patient, and then pulse oximetry or by blood gas analyses can be used to monitor the patient's oxygenation status.

The $O_2$_hemoglobin saturation can quite well be estimated by continuous measurement of pulse oxymetric saturation ($SpO_2$), which can be easily obtained. But the disadvantage is that there may be an important discrepancy between the blood $O_2$ saturation ($SaO_2$) and $SpO_2$ and that the measurement accuracy is much lower at lower SaO2. In addition, a precondition is that the patient has to have an adequate peripheral perfusion, or it is not so accurate.

$PaO_2$ might be continuously monitored by blood gas analysis or an arterial catheter. However, continuous $PaO_2$ required transducers which have to be inserted in an artery and are difficult to maintain if clotting around the catheter tip as well as

measurement drift. Therefore, it is seldom used in the ICU. Henceforth, frequent arterial blood samples and $PaO_2$ measurement via a blood gas analyzer are required. This is the most common oxygenation monitoring. It is important to consider that $PaO_2$ is different from tissue oxygenation in interpreting blood gas results. Furthermore, oxygenation, perfusion, and metabolism in different organs and tissues are very different. Thus, mixing different parameters and techniques to estimate the condition of ARDS patients is the key to monitor oxygenation. There are no studies to investigate the level of the lowest acceptable $PaO_2$. In the ARDSNet trials, they enrolled a large number of patients with the target oxygenation range of 55–80 mmHg. On the contrary, in one study cognitive impairment was found associated with $PaO_2$ levels <60 mmHg [17]. Thus, $PaO_2$ >60 mmHg may be adequate for the patients, but some other values need to be assessed including the patient's cardiac output (CO), hemoglobin level as well as metabolic demand. Maybe the oxygen transport ($DaO_2$) to the tissues is more comprehensive which include CO and hemoglobin level.

In addition, in most cases, mixed venous oxygen partial pressure ($PvO_2$) may be more important than $PaO_2$. Because it is primarily related to the oxygen tension in the tissues (but it should be noted that it reflects the mixing of oxygen tension in all organs and tissues).

As the physiologies of ARDS are dead space and intrapulmonary shunt, dead space can be assessed using volumetric capnography [15], while intrapulmonary shunt is related to alveolar flooding or lung atelectasis and can be assessed using the shunt equation requiring a pulmonary artery catheter (Details see above). The amount of $CO_2$ elimination in the lung is directly proportional to the alveolar ventilation. The elimination of pulmonary $CO_2$ can be monitored by volumetric exhaled $CO_2$ measurement (the $CO_2$ signal is integrated with the expired flow) for in-line or side stream infrared $CO_2$ analysis [18].

$CO_2$ elimination is dependent not only on the pulmonary circulation but also on the pulmonary ventilation as well as $CO_2$ production (i.e., metabolism). Thus, if $CO_2$ excretion has a sudden decrease at stable ventilation, this may lead to pulmonary perfusion to a sudden decrease, for example, pulmonary emboli or a reduction in cardiac output. Similarly, the reduction in $CO_2$ excretion without any change in circulation is due to deteriorated ventilation, e.g., at PCV reduced compliance (secretions edema or lung collapse) or increased airway obstruction by secretion.

## 6.3 Monitoring Respiratory Mechanics

The mechanics of the respiratory system correlate with the airway pressure, the pleural pressure, the flow rate, the lung volume, the tidal volume, and the condition of the lungs and chest wall. As a result, in a very heterogeneous lung in ARDS patients, the local strain (lung tissue deformation or volume change) and the transpulmonary pressure (airway pressure-pleural pressure) are different in different locations [19, 20]. It is important to pay attention that the outcome depends on the condition of the respiratory system and the patient position.

In short, the lung mechanics is the forces (i.e., pressures) required to inflate a certain amount of gas into the lung including two different parts: one is the force needed to overcome the resistance to airflow in the endotracheal tube and in the airways (flow-resistive pressure); the other one is the force requiring to overcome the elastic properties of the lungs and the chest wall (elastic recoil pressure).

### *6.3.1 Flow Resistance*

One important thing is to monitor flow resistance. Although some methods can be used to estimate flow resistance, some principles are important and need to keep in mind. First, resistance is dependent on the flow rate. Secondly, inspiratory resistance is different from expiratory resistance, and resistance depends on the patient's airways and a variable extent on the endotracheal tube resistance. There are two easy monitoring methods to monitor flow resistance: one is a computation of inspiratory resistance under a constant inspiratory flow:

$$\text{Flow resistance} = \frac{\left(\text{Peak pressure} - \text{Plateau pressure}\right)}{\text{Inspiratory flow rate}}$$

the other is an assessment of whether the flow has ceased at end-inspiration (during pressure-controlled ventilation) or at end-expiration. If not, this is because a time constant (resistance × compliance) of the system is too long for inspiratory and expiratory time according to the ventilator settings, respectively. In ARDS patients, this is due to either high resistance or too short expiratory time. Too short expiratory time has been used to induce auto-PEEP in order to keep the lungs open (inverse ratio ventilation) (Auto-PEEP is mentioned above).

### *6.3.2 Monitoring the Condition of Lung and Chest Wall*

Monitoring the condition of the lung and chest wall is the other important thing, such as plateau pressure, elastance, compliance, driving pressure, and so on. Lung and chest wall compliance, elastance can be obtained by all the parameters mentioned above, including VT, plateau pressure, PEEP, and so on (Details are below).

#### 6.3.2.1 Plateau Pressure

Assuming that all alveoli are opened, plateau pressure (Pplat) reflects end-inspiratory alveolar pressure [21]. A short end-inspiratory occlusion (0.3 s) is sufficient to estimate injurious pressure applied to the alveoli, especially in passive breathing. During spontaneous breathing, measuring Pplat might be possible also using an

end-inspiratory occlusion if no effort is detected, but this requires validation [22]. Pplat is strongly correlated with the risk of pneumothorax and other consequences of overdistension [23]. Boussarsar et al. found an increasing risk of pneumothorax when Pplat was greater than 35 $cmH_2O$ [23], and a safety limit of 30 $cmH_2O$ was deemed protective in a large randomized controlled trial [24]. However, Terragni and colleagues found with a Pplat greater than 28 $cmH_2O$ had a higher risk of overdistension on CT scan and higher proinflammatory cytokine levels in bronchoalveolar lavage than those with a lower Pplat [25] at patients in a cohort of patients with ARDS ventilated with a Pplat below 30 $cmH_2O$. Nowadays, maintaining Pplat at or below 28 $cmH_2O$ as used in a large trial seems to be a reasonable and safe threshold.

#### 6.3.2.2 Elastance and Compliance

Suter and colleagues first used the beat oxygen delivery to titrate the PEEP level [26]. They found that the best oxygen delivery was associated with the best compliance of respiratory system ($C_{RS}$), suggesting that compliance could be used to set the level of optimal PEEP. Grasso and colleagues reported different effects of high PEEP levels on $C_{RS}$ according to the lung recruitability [27]. The $C_{RS}$ depends on the lung recruitability. However, one major caveat of $C_{RS}$ is that it may be artificially increased by intratidal recruitment. Therefore, repeated lung and airway opening and closing need to be avoided, or setting PEEP according to the best $C_{RS}$ could be very misleading.

#### 6.3.2.3 Driving Pressure (ΔP)

Ventilation with a $\Delta P$ value below 20 $cmH_2O$ was associated with a lower risk of pneumothorax as compared with conventional ventilation with large tidal volumes [28]. In a post hoc analysis of large randomized trials, Amato and colleagues found that a $\Delta P$ value greater than 14–15 $cmH_2O$ was independently associated with higher mortality [29]. Moreover, beneficial effects of VT reduction or high PEEP levels on mortality were mediated by a decrease in $\Delta P$. However, whether a ventilation strategy according to $\Delta P$ would result in better outcomes is still unknown.

#### 6.3.2.4 Transpulmonary Pressure (PL) and Esophageal Pressure

At end-inspiration, PL is a more reliable measurement of the distending pressure of the lung than Pplat. Because Pplat depends not only on PL, but also on pleural pressure (Ppl). Indeed, in some patients, Ecw is responsible for almost 50% of the $E_{RS}$, while in other cases is approximately 15–20% [30]. Grasso and colleagues [31] enrolled 14 patients with refractory ARDS referred for consideration of extracorporeal membrane oxygenation (ECMO). They were all ventilated with a Pplat greater than 30 $cmH_2O$. Half of them had PL at end-inspiration (PL,ei) below 25 $cmH_2O$,

suggesting a significant contribution of the chest wall to the increase Pplat. Increasing PEEP up to a PL,ei of 25 improved oxygenations without the need for ECMO. PL,ei might also be assessed in spontaneous breathing patients with an esophageal balloon catheter doing an end-inspiratory occlusion [32].

PL at end-expiration (PL,ee) is the pressure distending the lungs at end-expiration. Negative PL,ee values are common in ARDS, potentially favoring cyclic reopening and closing of alveoli during ventilation and atelectrauma [33]. In ARDS, setting PEEP to a positive PL,ee was associated with improved physiological parameters and was well tolerated compared with setting PEEP according to an oxygenation Table [34]. However, the absolute value of esophageal pressure reflects the pleural pressure at mid-chest [35]. Different part of the chest has different Ppl, which can be monitored by esophageal pressure (Details are above). In addition, it does not specifically indicate whether the lung is recruitable or not.

Recently, Yoshida and coworkers carried out a study to confirm the validity of the esophageal pressure to assess regional pleural pressure in pigs and human cadavers embalmed to preserve tissue elasticity [35]. The Ppl gradient between the nondependent and the dependent part of the chest was higher in pigs with injured lungs than healthy lungs, which may indicate higher in human cadavers (around 10 $cmH_2O$) confirm Ppl heterogeneity. PL calculated using esophageal pressure was reliable; however, it was not reliable in calculating the Ppl in the nondependent and the dependent part of the chest cavity [35]. Moreover, the elastance-derived method was a good surrogate to calculate PL,ei for the actual PL in the nondependent part of the chest cavity. Therefore, the use of PL using the elastance-derived method may be used to estimate the risk of overdistension in the nondependent part of the lung, while the use of absolute values reflects pleural pressure at mid-chest.

#### 6.3.2.5 Work of Breathing and Esophageal Pressure–Time Product

Work of breathing (WOB) is the energy expenditure of respiratory muscles to generate a volume. And Campbell diagram can be used to calculate WOB as the area enclosed by the product of the change in Pmus and change in volume. WOB per minute can be calculated (in joules per minute [J/min]) and normalized to the tidal volume (effort per unit of volume displaced, in joules per liter [J/L]). In healthy subjects at rest, WOB ranges from 2.4 to 7.5 J/min and from 0.2 to 0.9 J/L [36].

#### 6.3.2.6 End-Expiratory Lung Volume

It is recommended that end-expiratory lung volume (EELV) can be measured to evaluate whether the lung is collapsed or overinflated and to set or assess the effect of PEEP. EELV could be assessed by CT scan and CT is the golden tool to measure EELV. But CT is cumbersome and has radiation risk at frequent repeated exposure. Therefore, CT cannot be used as a monitoring routine tool at bedside, and especially

for monitoring EELV or its changes, such as recruitment and overdistention by different interventions.

Another way is gas dilution techniques. However, the limitation of the tracer gas dilution techniques is the closed-circuit method, which requires patient disconnecting from the ventilator. This disadvantage makes this technology hardly as a monitor technique. Because of this disadvantage, an improved method, open-circuit multi breathing nitrogen well flushing technology, is proposed. In contrast, it is now incorporated in one ventilator brand is quite easy to handle and gives acceptable estimates of EELV [37]. However, one thing should be considered that the obtained EELV is only the volume in lungs. If EELV increases with PEEP, it is important to determine whether the increase in EELV is due to overinflation of open units, increased in normal lung volume, or recruiting previously collapsed lung units or a combination of all.

#### 6.3.2.7 Mechanical Power

Mechanical power is the combination of pressure, volume, flow, and respiratory rate, which may be a more reliable predictor of VILI. 12 J/min may be a meaningful threshold of VILI, and may be a predictor of mortality and survival. What is more, mechanical power may be a predictor of mortality (For details refer to Chap. 2).

The aim of mechanical ventilation is to provide adequate gas exchange without further injuries to the lungs and other organs. Lung mechanics (such as pressures, volumes, and flow) and lung imaging enable the clinician to ensure they provide as much lung-protective ventilation as possible. Lung mechanics monitoring is very important to avoid VILI.

## 6.4 Monitoring by Lung Imaging

ARDS lungs are very heterogeneous and it is not possible to assess the regional differences in lung mechanical properties with conventional lung mechanics. Physiological respiratory parameters cannot provide regional information. For this reason, the other choices are chest CT or electrical impedance tomography (EIT). CT is a golden method to provide regional ventilation information. However, CT is an excellent method for diagnosis and understanding of the underlying deterioration in lung morphology, but too demanding for monitoring [38]. It is impossible using CT for monitoring at bedside. On the other hand, EIT is more useful for monitoring and evaluating the regional effects of PEEP, recruitment maneuvers, and ventilation [39]. EIT is no-radiation, dynamic, and simple way for monitoring. And EIT can provide different regional information, including ventilation distribution, the percentage of overdistention and collapse, center of ventilation, and so on.

Another useful method is lung and diaphragm ultrasound, which is suitable to diagnose lung consolidation and pleural conditions [40]. Lung ultrasound is a

bedside method, which is developing rapidly in the recent years. Lung ultrasound is ideal for both diagnosing and intermittent monitoring. What is more, the ultrasound is easy to get and can be used at bedside. Diaphragm ultrasound allows the noninvasive quantification of inspiratory efforts during assisted ventilation using a linear probe (>10 MHz) positioned on the zone of apposition of the diaphragm. The measurement of diaphragm ultrasound has been validated in critically ill patients [41].

## 6.5 Monitoring of Adequate PEEP by Lung Mechanics Monitoring

PEEP setting is a difficult ventilation element to choose. There are lots of methods for selecting optimal PEEP. An optimal PEEP is a pressure at end-expiratory, which should be set at an end-expiratory pressure that prevents: expiratory collapse, intratidal collapse, and re-expansion (recruitment-derecruitment); and end-expiratory and end-inspiratory overdistension. It is essential to ARDS patient; however, still not set using suitable methods. Also, since in ARDS the lung is very heterogeneous, in other words, lung regions close to each other have extremely different specific lung volumes and compliances [20], the general methods setting PEEP are always a compromise and could never be completely "optimal."

Based on lung mechanics, there are many approaches to select PEEP. Exclued lung imaging methods, the most common methods for PEEP setting all use respiratory mechanics. Static pressure-volume curve is the classical way to set PEEP. PEEP is set at the pressure where inspiratory compliance increases, which can be revealed by the "lower inflection point" (LIP). Ventilation operates on the steep part of P-V curve, between LIP and the pressure at the "upper inflection point" (UIP), when compliance suddenly decreases, indicating excessive expansion. However, the most important pressure is the pressure at which a large number of lung regions begin to collapse, and this pressure occurs on the expiratory limb of the loop, where compliance is maximal.

Another method is based on the oxygenation goal (ARDS network PEEP/$FIO_2$ table) proposed by ARDSNet. PEEP according to the PEEP/$FIO_2$ table of the National Institutes of Health ARDS network trial [42] (PEEP/$FIO_2$ table), PEEP and $FIO_2$ were titrated to maintain $PaO_2$ between 55 and 80 mmHg or $SpO_2$ between 88% and 95%. This is the most common way to select PEEP. However, this method just considers the oxygenation but ignores lung and chest wall condition.

As P-V curve has some limitations, there are some other technologies to select PEEP. A PEEP trial can estimate similar pressure as reducing or increasing PEEP slowly after a maximum recruitment is performed [43]. The pressure with best or highest $C_{RS}$ (or lowest $\Delta P$) is found and the "optimal" PEEP is 2 $cmH_2O$ above the pressure, which is CRS-related method or $\Delta P$-related method. However, this kind of maneuver is only useful if the lungs can be recruited, mainly in early ARDS. Non-recruitment patients may have no highest $C_{RS}$ or lowest $\Delta P$.

Another selection may be stress index (SI). Since time shows a linear volume increase at a constant flow, SI can be considered as a tidal volume/pressure curve,

that is, the instant slope of the curve equaling to the Ers if the resistance is constant. Therefore, the slope (SI > 1) and volume increasing over time indicate that Ers increases, i.e., overinflation. In contrast, a decrease in slope (SI < 1) indicates a decrease in Ers, such as tidal volume recruitment, while a straight line (SI = 1) indicates that Ers is constant. Although physiologically reasonable, it is not clear whether PEEP can reduce VILI or improve outcome.

Except all these methods, there are still some methods according to lung mechanics, such as the ExPress trial [44]: PEEP was adjusted to reach a Pplat between 28 and 30 $cmH_2O$, transpulmonary pressure, and esophageal pressure. They all have their advantages and disadvantages.

With the development of technology, EIT can be used to select optimal PEEP. And it may be the simplest way at bedside. There are many EIT parameters to select PEEP. The simplest way is to use the center of ventilation (COV) representing the distribution of ventilation across the chest from the ventral to dorsal [45–47]. If most ventilation moves in the ventral region and PEEP increases, a shift of COV from ventral to dorsal regions indicates that PEEP has a positive response. During the decremental PEEP maneuver, another way to assess the risk of atelectasis is to observe the change in end-expiratory lung impedance (ΔEELI) over time [48], or regional ventilation delay (RVD) [49]. When PEEP is reduced, there is always an associated decrease in EELV (and in EELI) which will be much greater if associated with derecruitment. Setting PEEP above the level associated with a decrease in ΔEELI of 10% during a decremental PEEP trial resulted in improved oxygenation and lower ΔP compared with PEEP setting according to the low $PEEP/FIO_2$ table in 16 patients with a baseline $PaO_2/FIO_2$ below 300 mmHg [48]. RVD is a measure of tidal recruitment in passively breathing patients. Areas of repetitive opening and closing of alveolar units would likely have delays, the higher the value the greater degree of tidal recruitment. Monitoring ventilation distribution now is available to quantify the degree of regional compliance changes when PEEP is titrated. Compliance changes relative to each PEEP is graphically computed to demonstrate compliance loss related to high PEEP (i.e., overdistension) and low PEEP (i.e., collapse), which is so-called Costa's method to calculate the percentage of overdistention and collapse [50]. The lowest sum of collapse and overdistension will be the optimal PEEP, which will lead to less lung injury. This point of intersection may represent the balance of risk versus benefit. Recently, some researches carried out trials using this method selecting optimal PEEP.

## 6.6 Monitoring Airway Closure

Small airway injury was found in experimental and autopsy studies in ARDS [51]. This can be interpreted as the results of repeated airway opening and closing during tidal breaths at low PEEP levels. Chen and colleagues [52] conducted a study based on the analysis of low-flow inflation *P–V* curves in ARDS. The study gave attention to that in about 1/3 of patients, the initial part of the slope can be superimposed to the *P–V* curve of a blocked circuit indicating complete closure of the airways.

However, the esophageal pressure is unchanged during that period whereas airway pressure increases dramatically [52]. Therefore, this may indicate complete airway closure while the "baby lung" remains aerated on the chest CT scan. Respiratory monitoring can help clinicians discover airway closure as early as possible to avoid lung injury.

## 6.7 Monitoring Dyssynchrony

Dyssynchrony will occur as an appropriate ventilation setting. It is essential to distinguish all kinds of dyssynchrony. Clinical assessment by visual observation will provide many important information on patient's synchrony. The ventilator's screen displays flow, Paw, and tidal volume waveforms which can be sufficient to diagnose some dyssynchronies [53]. Nevertheless, more precise detection can be obtained using additional monitoring tools such as esophageal balloon or electrical activity of the diaphragm (EAdi). Esophageal pressure is directly dependent on respiratory muscle activity with granting dyssynchrony assessment. EAdi can be displayed on a ventilator screen along with the other waveforms providing useful information on patient's neural respiratory times and its synchrony with ventilator delivery. This is a minimally invasive way to monitor patient–ventilator dyssynchrony as most of the ventilated ICU patients require a feeding tube (details see above).

## 6.8 Conclusion

Mechanical ventilation is life-saving for ARDS patients and provides a unique window on the lung pathophysiology on which management should be guided. Additional tools such as esophageal pressure monitoring, electrical activity of the diaphragm, or bedside lung imaging by EIT add a lot to our understanding and for delivering a personalized approach to mechanical ventilation. It is possible to prevent VILI and maintain acceptable gas exchange according to the obtained information from respiratory system monitoring, such as gas exchange, lung mechanics, and imaging monitoring. With respiratory monitoring, precise mechanical ventilation will come soon. It can provide an individual ventilation setting in order to avoid unnecessary lung injury.

## References

1. Gattinoni L, Quintel M. Fifty years of research in ARDS why is acute respiratory distress syndrome so important for critical care? Am J Respir Crit Care Med. 2011;194(9):1051–2.
2. Definition Task Force ARDS, Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33.

3. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315(08):788–800.
4. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369(22):2126–36.
5. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
6. Falke KJ, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver MB. Ventilation with end-expiratory pressure in acute lung disease. J Clin Invest. 1972;51(09):2315–23.
7. Maunder RJ, Shuman WP, McHugh JW, Marglin SI, Butler J. Preservation of normal lung regions in the adult respiratory distress syndrome. Analysis by computed tomography. JAMA. 1986;255(18):2463–5.
8. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med. 2005;31(06):776–84.
9. Gammon RB, Shin MS, Groves RH Jr, Hardin JM, Hsu C, Buchalter SE. Clinical risk factors for pulmonary barotrauma: a multivariate analysis. Am J Respir Crit Care Med. 1995;152(4, Pt1):1235–40.
10. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis. 1988;137(05):1159–64.
11. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest. 1997;99(05):944–52.
12. Dhainaut JF, Devaux JY, Monsallier JF, Brunet F, Villemant D, Huyghebaert MF. Mechanisms of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. Chest. 1986;90(01):74–80.
13. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. Intensive Care Med. 2016;42(05):862–70.
14. Dantzker DR, Brook CJ, Dehart P, Lynch JP, Weg JG. Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am Rev Respir Dis. 1979;120(05):1039–52.
15. Radermacher P, Maggiore SM, Mercat A. Fifty years of research in ARDS. Gas exchange in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;196(08):964–84.
16. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med. 2002;346(17):1281–6.
17. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185:1307–15.
18. Suarez-Sipmann F, Bohm SH, Tusman G. Volumetric capnography: the time has come. Curr Opin Crit Care. 2014;20:333–9.
19. Chiumello D, Carlesso E, Cadringher P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med. 2008;178:346–55.
20. Perchiazzi G, Rylander C, Derosa S, et al. Regional distribution of lung compliance by image analysis of computed tomograms. Respir Physiol Neurobiol. 2014;201:60–70.
21. Loring SH, Topulos GP, Hubmayr RD. Transpulmonary pressure: the importance of precise definitions and limiting assumptions. Am J Respir Crit Care Med. 2016;194(12):1452–7.
22. Bellani G, Grassi A, Sosio S, Foti G. Plateau and driving pressure in the presence of spontaneous breathing. Intensive Care Med. 2019;45(01):97–8.
23. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. Intensive Care Med. 2002;28(04):406–13.
24. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8.
25. Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2007;175(02):160–6.

26. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med. 1975;292(06):284–9.
27. Grasso S, Fanelli V, Cafarelli A, et al. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171(09):1002–8.
28. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(06):347–54.
29. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(08):747–55.
30. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med. 1998;158(01):3–11.
31. Grasso S, Terragni P, Birocco A, et al. ECMO criteria for influenza a (H1N1)-associated ARDS: role of transpulmonary pressure. Intensive Care Med. 2012;38(03):395–403.
32. Mezidi M, Guérin C. Complete assessment of respiratory mechanics during pressure support ventilation. Intensive Care Med. 2019;45(04):557–8.
33. Talmor D, Sarge T, O'Donnell CR, et al. Esophageal and transpulmonary pressures in acute respiratory failure. Crit Care Med. 2006;34(05):1389–94.
34. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359(20):2095–104.
35. Yoshida T, Amato MBP, Grieco DL, et al. Esophageal manometry and regional transpulmonary pressure in lung injury. Am J Respir Crit Care Med. 2018;197(08):1018–26.
36. Mancebo J, Isabey D, Lorino H, Lofaso F, Lemaire F, Brochard L. Comparative effects of pressure support ventilation and intermittent positive pressure breathing (IPPB) in non-intubated healthy subjects. Eur Respir J. 1995;8(11):1901–9.
37. Dellamonica J, Lerolle N, Sargentini C, et al. Accuracy and precision of end-expiratory lung-volume measurements by automated nitrogen washout/washin technique in patients with acute respiratory distress syndrome. Crit Care. 2011;15:R294.
38. Simon M, Braune S, Laqmani A, et al. Value of computed tomography of the chest in subjects with ARDS: a retrospective observational study. Respir Care. 2016;61:316–23.
39. Frerichs I, Amato MB, van Kaam AH, et al. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group. Thorax. 2017;72:83–93.
40. Lichtenstein D, Goldstein I, Mourgeon E, et al. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. Anesthesiology. 2004;100:9–15.
41. Vivier E, Mekontso Dessap A, Dimassi S, et al. Diaphragm ultrasonography to estimate the work of breathing during noninvasive ventilation. Intensive Care Med. 2012;38(05):796–803.
42. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
43. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37:2642–7.
44. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299:646–55.
45. Frerichs I, Dargaville PA, van Genderingen H, Morel DR, Rimensberger PC. Lung volume recruitment after surfactant administration modifies spatial distribution of ventilation. Am J Respir Crit Care Med. 2006;174(07):772–9.
46. Yoshida T, Engelberts D, Otulakowski G, et al. Continuous negative abdominal pressure: mechanism of action and comparison with prone position. J Appl Physiol (1985). 2018;125(01):107–16.

47. Yoshida T, Engelberts D, Otulakowski G, et al. Continuous negative abdominal pressure reduces ventilator-induced lung injury in a porcine model. Anesthesiology. 2018;129(01):163–72.
48. Eronia N, Mauri T, Maffezzini E, et al. Bedside selection of positive end-expiratory pressure by electrical impedance tomography in hypoxemic patients: a feasibility study. Ann Intensive Care. 2017;7(01):76.
49. Blankman P, Hasan D, Erik G, Gommers D. Detection of 'best' positive end-expiratory pressure derived from electrical impedance tomography parameters during a decremental positive end-expiratory pressure trial. Crit Care. 2014;18(03):R95.
50. Costa ELV, Borges JB, Melo A, et al. Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. In: Pinsky M, Brochard L, Hedenstierna G, Antonelli M, editors. Applied physiology in intensive care medicine, vol. 1. Berlin, Heidelberg: Springer; 2012. p. 165–70.
51. Morales MMB, Pires-Neto RC, Inforsato N, et al. Small airway remodeling in acute respiratory distress syndrome: a study in autopsy lung tissue. Crit Care. 2011;15(01):R4.
52. Chen L, Del Sorbo L, Grieco DL, et al. Airway closure in acute respiratory distress syndrome: an underestimated and misinterpreted phenomenon. Am J Respir Crit Care Med. 2018;197(01):132–6.
53. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient–ventilator asynchronies. Intensive Care Med. 2006;32(01):34–47.