Mechanical ventilation during acute lung injury: Current recommendations and new concepts

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Summary

Despite a very large body of investigations, no effective pharmacological therapies have been found to cure acute lung injury. Hence, supportive care with mechanical ventilation remains the cornerstone of treatment. However, several experimental and clinical studies showed that mechanical ventilation, especially at high tidal volumes and pressures, can cause or aggravate ALI. Therefore, current clinical recommendations are developed with the aim of avoiding ventilator-induced lung injury (VILI) by limiting tidal volume and distending ventilatory pressure according to the results of the ARDS Network trial, which has been to date the only intervention that has showed success in decreasing mortality in patients with ALI/ARDS. In the past decade, a very large body of investigations has determined significant achievements on the pathophysiological knowledge of VILI. Therefore, new perspectives, which will be reviewed in this article, have been defined in terms of the efficiency and efficacy of recognizing, monitoring and treating VILI, which will eventually lead to further significant improvement of outcome in patients with ARDS.

The most severe forms of acute respiratory failure, such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), are relatively common in the ICU setting [1]. The estimated crude incidences for ALI and ARDS in the United States are 78.9 and 58.7 cases per 100,000 persons/year respectively, higher than previous reported [1,2]. Projections suggest that as the population ages there will be a further increase in the incidence in the United States from 190,000 patients/year to 300,000/year in 2025–2030 [2]. Furthermore, the incidence will likely increase dramatically during the outbreaks of acute viral infections such as SARS and H1N1.

The first description of ARDS appeared in 1967, in a paper by Ashbaugh et al. which described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decrease lung compliance, and diffuse infiltrates on the chest radiography [3]. Several clinical disorders have

been associated with the development of ALI/ARDS; the most common cause is severe sepsis, which may be associated with pneumonia or a non-pulmonary infectious source. Other major causes of ALI/ARDS include aspiration of gastric contents, hemorrhage and shock following major trauma, and several other less common causes such as severe acute pancreatitis, transfusion-associated lung injury, and drug reactions [4,5].

In 1994, an American–European Consensus Conference (AECC) standardized the definition for ALI and ARDS [6] on the basis of the following clinical parameters: acute onset of severe respiratory distress; bilateral infiltrates on frontal chest radiograph; absence of left atrial hypertension, a pulmonary capillary wedge pressure $\leq$ 18 mmHg, or no clinical signs of left heart failure; and severe hypoxemia (ALI, partial arterial pressure of oxygen/fraction of inspired oxygen ratio [PaO_2/FiO_2] ratio $\leq$ 300 mmHg; mmHg; ARDS, PaO_2/FiO_2 ratio $\leq$ 200 mmHg). Although the AECC definition played a historical role in providing standardized entry criteria, they have often been criticized and questioned [7–9]. First of all, the clinical criteria for ALI/ARDS reflect nonspecific functional abnormalities of the respiratory system and do not necessarily predict diffuse alveolar damage (DAD). Patel et al. [10] looked at patients who initially presented with the consensus definition of ALI/ARDS and found that 60% of all open-lung biopsies performed in these patients did not reveal the presence of DAD and the results of the biopsy changed the therapy. These patients underwent biopsy because the diagnosis was uncertain. Moreover, two clinicopathological confrontation studies showed that only 50% and 66% of patients respectively with clinical diagnosis of ARDS had DAD [11]. Furthermore, the AECC definition does not take into consideration the epidemiological and heterogeneous background of ARDS [12]. The distinction between pulmonary ARDS and extrapulmonary ARDS could have significant clinical implications, as patients might respond differently to various treatments including mechanical ventilation [13,14]. However, a meta-analysis of Agarwal et al.

has recently suggested that there is no difference in mortality between these two groups [15]. Moreover, Thille et al. has showed that this classification is uncertain in more than one third of patients and that, after few days of mechanical ventilation, alveolar recruitment in response to a positive end-expiratory pressure (PEEP) is similar in pulmonary and extrapulmonary ARDS [16]. On the other hand, specific subsets of these groups (such as sepsis and aspiration pneumonia) have been associated with the highest mortality, whereas patients with trauma-related lung injury have a lower risk of death [17–20]. Moreover, the level of applied PEEP may affect the classification of acute respiratory failure. In one study, PEEP at 10 cmH_2O allowed better differentiation of ARDS and ALI. After the PEEP trial, about one third of patients initially classified as having ARDS were reclassified as having ALI, and 9% had a PaO_2/FiO_2 ratio > 300 mmHg. The mortality rates for reclassified categories were 45% for ARDS, 20% for ALI, and 6% for others [21]. Another issue rising from the AECC definition is that it does not take into account the co-existence of organ failure. Several investigators have demonstrated that multi-organ failure (MOF), either as the predisposing condition or as a consequence of ARDS, and not unsupportable respiratory failure, is the leading cause of death in ARDS [22]. Stapleton et al. studied consecutive cohorts of patients with ARDS (n = 462) from 1982 till 1998, using prospectively defined and identical definitions of MOF and respiratory failure [23]. Overall, sepsis and MOF were the most frequent causes of death (30–50%), while unsupportable respiratory failure was identified as the cause of death in 13–19% of the cases. In an international study on the variability of mechanical ventilation management in patients with ARDS, the logistic regression multivariable analysis confirmed that high severity of illness and organ dysfunction were the strongest independent predictors of death in the 467 ARDS patients recruited into the study. In this analysis, oxygenation failure was associated with a negative outcome, which, as the authors stated, does not imply that improvement in oxygenation is a predictor of good outcome [22]. Thus, ARDS must be perceived as a systemic disease, and its management/prevention must focus also on the identification and treatment of causal factors and on the systemic management of the patient in order to prevent ARDS development and other organ failure [24,25]. ALI/ARDS-associated mortality rates, although significantly improved, remain impressively high. A recent study reported that the pooled mortality from ALI/ARDS from 1994 to 2006 was 44.0% (95% CI, 40.1–47.5) in observational studies, and 36.2% (95% CI, 32.1–40.5) in randomized controlled trials [26].

Current recommendations: from aiming at normal oxygenation and ventilation to avoiding ventilator-induced lung injury

Despite a very large body of research directed at increasing our understanding and at improving the management of ALI/ARDS [27–32], no effective pharmacological therapies have been

Glossary

AECC	American–European Consensus Conference
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
DAD	diffuse alveolar damage
ECMO	extracorporeal membrane oxygenation
EIT	electrical impedance tomography
FRC	functional residual capacity
HFO	high frequency oscillatory
HFP	high frequency percussive
MOF	multi-organ failure
NAVA	neurally adjusted ventilatory assist
NIV	noninvasive mechanical ventilation
NMBA	neuromuscular blocking agents
PEEP	positive end-expiratory pressure
RM	recruitment maneuver
VILI	ventilator-induced lung injury

found, and supportive care with mechanical ventilation remains the cornerstone of treatment [33]. In the past, traditional approaches to mechanical ventilation have used tidal volumes of 10 to 15 mL/kg of body weight [34]. These volumes are larger than those in normal subjects at rest (range, 7–8 mL/kg), but they are frequently necessary to achieve normal values of arterial carbon dioxide partial pressure and pH. However, since 1970s several experimental and clinical studies showed that mechanical ventilation, especially at high tidal volumes and pressures, can cause or aggravate ALI, the so-called ventilator-induced lung injury (VILI) [35,36]. VILI results from the action of mechanical forces on lung structures such as the epithelial cells, the endothelial cells, the extracellular matrix, and the peripheral airways during mechanical ventilation. In particular, cyclic over-distension and collapse/re-opening of airway units with each breath are two key pathophysiological mechanisms leading to VILI [37]. Over-distension is caused by excessive transpulmonary pressure. The injury due to this mechanism has been termed barotrauma or volutrauma. Cyclic collapse of the alveoli and small airways occurs in those lung regions where the end-expiratory pressure is inadequate to prevent their de-recruitment (atelectrauma); the reopening of these units generates an injurious shear stress. Of note, there is some controversy on the real clinical impact of this mechanism [38]. In 1998, Tremblay and Slutsky [39] coined the term ''biotrauma'' to describe the pulmonary and systemic inflammatory response triggered by lung cell distension, disruption, and/or necrosis after application of mechanical ventilation. The injury induced by mechanical ventilation originates in the lung, but it may also affect distal organs by release of mediators from the lung into the systemic circulation. This de-compartmentalization of VILI is presumably one of the causes of MOF occurring in patients with ALI/ARDS resulting in higher mortality rates [40].

VILI is typically thought to worsen ALI or ARDS, which result from several possible lung and systemic diseases. However, there are interesting evidences suggesting that VILI may occur also in healthy lungs. Gajic et al. showed that, out of 332 mechanically ventilated patients without ALI, 80 developed ALI and, interestingly, one of the independent risk factor associated with this evolution was the application of large tidal volumes (odds ratio 1.3 for each mL above 6 mL/kg predicted body weight, $P < 0.001$) [41]. The same results were found from another investigation on a larger patient population with similar characteristics [42]. Moreover, high tidal volume was found to be an independent risk factor for ALI development (odds ratio 5.4, 95% confidence interval 1.54–19.24) also in patients with severe brain injury [43], and it was associated with poor outcome. The authors hypothesized that, following the primary brain injury, the occurring of a systemic inflammatory reaction may prime the lung, which become more susceptible to the mechanical stress induced by an injurious ventilation strategy: a clinical example of the so called double hit model of VILI [44].

In order to minimize VILI, the Consensus Conference in 1994 recommended that plateau pressure should generally be limited to 35 cmH$_2$O [45]. However, little change in ventilator practice occurred until publication of the ARDS Network study [27], which demonstrated that a lung protective strategy decreases mortality in patients with ALI. The ARDS Network study demonstrated an absolute risk reduction in short-term mortality of nearly 9% in patients receiving a pressure- and volume-limited strategy. This attempt to avoid volutrauma and barotrauma relies on using low tidal volume ($\leq$ 6 mL/kg of predicted body weight [PBW]) ventilation, and limiting transpulmonary distending pressure (i.e., plateau pressure $\leq$ 30 cmH$_2$O after a 0.5-second end-inspiratory pause). Moreover, the application of PEEP, based on a predefined table coupling progressively increasing PEEP values with increasing inspired fraction of oxygen requirements, is meant to prevent atelectrauma [46]. To date, the ARDS Network trial is the only intervention that has showed success in decreasing mortality in patient with ALI/ARDS [27], and has defined the current recommendations on the ventilatory strategy to be applied in these patients.

Limitations of the current recommendations

Despite the recommendation of using pressure- and volume-limited ventilatory strategies, VILI may still persist or progress in some patients, resulting in worse outcome.

Lack of adherence to guidelines may be one of the reasons. In fact, Sakr et al. showed in an European multicenter observational study that, 4 years after the publication of the ARDS Network trial, out of 398 patients with ALI or ARDS only 44% received mechanical ventilation with a tidal volume in the range of 5 and 7 mL/kg of PBW, whereas about 9% of them received a tidal volume $\geq$ 12 mL/kg of PBW [47]. These data were confirmed by another North-American observational study showing a proportion of only 16% of patients with ALI or ARDS receiving a tidal volume $\leq$ 8 mL/kg PBW 12 months after the ARDS Network recommendations were provided [48].

Moreover, it is still unclear whether the current recommendations of delivering tidal volumes as low as 6 mL/kg and keeping plateau pressures < 30 cmH$_2$O are safe enough, or a further reduction of these thresholds would be more protective, leading to an additional improvement in survival of ALI or ARDS.

In this regard, Terragni and al. [49] demonstrated that about one third of patients with severe ARDS, who were ventilated according to the ARDS Network recommendations, had evidence of alveolar overdistension based on CT scan of the chest. These data were in accord with the analysis of Hager et al. suggesting that a plateau pressure of 30 cmH$_2$O in some patients may be too high to be lung protective [50].

Furthermore, beside the controversies on defining optimal tidal volume and plateau pressure, the setting of PEEP is also a source of significant debate, since there are still significant issues in establishing the optimal PEEP threshold that is

considered safe in all patients with ALI/ARDS. PEEP is a simple physiological intervention but itself has potentially deleterious effects on right and left ventricular function, pulmonary vascular resistance, and thoracic compliance, leading to unpredictable impairment of gas exchange and hemodynamics. Airway pressures necessary to recruit collapsed lung areas can improve oxygenation but can also overdistend normal areas of pulmonary parenchyma and worsen inflammation [51].

The currently available evidence does not clearly indicate the best method to select PEEP. A PEEP setting of 0 cmH$_2$O generally is accepted to be harmful in the patient with ARDS and experimental data suggest that PEEP levels exceeding traditional values of 5 to 12 cmH$_2$O can minimize the shearing injury to the lungs in patients with considerable edema and alveolar collapse [52,53]. At least three multicenter, randomized controlled trials evaluating the benefits of a protocolized higher PEEP strategy in a broad range of patients already receiving pressure- and volume-limited ventilation have not demonstrated a survival advantage with this type of ''open-lung ventilation strategy'' [30,31,54]. However, each of these studies reported a higher PaO$_2$/FiO$_2$ ratio in the higher PEEP group. Moreover, in two of the studies, despite the use of a different method to obtain in the experimental groups a higher PEEP within an open-lung ventilation strategy (PEEP titrated on oxygenation by FiO$_2$: PEEP charts [31] versus PEEP titrated to obtain a plateau pressure less than 30 cmH$_2$O [30]) a significant improvement in secondary end-points was found: lower rates of refractory hypoxemia, death with refractory hypoxemia, and use of rescue therapies [30,31]. Recently, Briel et al. [55], in a systematic review and meta-analysis of individual-patient data, using primary data from these trials, demonstrated that, after adjusting for individual patient covariates, higher PEEP was associated with a reduction in hospital mortality (adjusted RR, 0.90; 95% CI, 0.81–1.00), which just met the accepted statistical criterion for significance ($P = 0.049$) among the subset of patients with ARDS. On the other hand, in patients with less severe hypoxemia (PaO$_2$/FiO$_2$ ratio > 200 mmHg) there was no significant association between higher levels of PEEP and clinical benefit. The authors also observed a small increased risk of pneumothorax (absolute risk difference, 1.6%) for patients with ARDS treated with higher PEEP, but no other evidence suggesting serious adverse effects associated with higher PEEP in patients with ARDS was found. Thus this meta-analysis, showing the potentially lower hospital mortality and the absence of increased serious adverse events associated with higher PEEP levels in patients with ARDS, support the use of higher PEEP in these patients. However, to the questions ''How much PEEP in ALI?'' and ''How to titrate PEEP?'', the authors can only provide vague answers [51]. Moreover, it is not clear, given the current evidence, whether PEEP titration in ARDS patients should be guided by a defined protocol or whether the ventilatory strategy should be individualized to the specific respiratory system mechanics of the patient [51,56].

New concepts

Although the only clinical trial showing a significant decrease of the mortality rate for patients with ALI or ARDS has been published already more than 10 years ago, a very large body of investigations conducted in the last decade has determined significant achievements on the pathophysiological knowledge of VILI. New perspectives have been defined in terms of the efficiency and efficacy of recognizing, monitoring and treating VILI, which will eventually lead to further significant improvement in ARDS patients outcome. *Table I* summarizes the ongoing clinical trials on VILI.

The role of lung stress and strain in ventilator-induced lung injury

The main physiopathological mechanisms of VILI, such as barotrauma and volotrauma, have been revisited by a recent interesting study by Chiumello et al. [57]. They reasoned that potential clinical determinants of VILI are high transpulmonary pressure and/or high ratio between tidal volume and functional residual capacity (FRC) respectively, rather that simply high plateau airway pressures and high tidal volumes. The authors defined stress as the change in distending pressure of the lung, according to the following equation: $\Delta PL = \Delta PAW \times EL/(EL + ECW)$. ΔPL is change in transpulmonary pressure, ΔPAW corresponds to the change in plateau pressure (assuming no respiratory efforts), EL is the elastance of the lung, and (EL + ECW) is the elastance of the respiratory system, which is the sum of the lung elastance plus the chest wall elastance (ECW). Transpulmonary pressure was estimated measuring the esophageal pressure. Strain was defined as the ratio (ΔV/FRC) of the lung volume change (ΔV) induced by the application of tidal volume or ΔPAW over the FRC.

Stress and strain in the lung are physiologically linked by the following equation: $\Delta PL(stress) = Especific-L \times \Delta V/FRC(strain)$, where Especific-L is the specific lung elastance and corresponds to the transpulmonary pressure at which FRC doubles.

Stress and strain were measured in 50 patients with ALI or ARDS and compared with data from surgical patients without lung injury [57]. Interestingly, the relationship between plateau pressure and transpulmonary pressure did not have the same slope in every patient due to different elastance of the chest wall, and, due to variability in FRC, lung strain measurement was widely distributed even with the same applied tidal volume based on PBW and PEEP. This analysis, although characterized by some limitations, strongly suggests that tidal volume and plateau pressure per se are very approximate and imprecise indicators of dynamical lung mechanical properties. Prospective clinical studies using defined thresholds of stress and strain are needed to confirm the clinical impact of this strategy on ARDS patient outcome.

TABLE I

Title of the ongoing clinical trials on ventilator-induced lung injury (VILI), the location of the coordinating center and the identification number

Location	Title of the clinical study	Type of study	Identification number
St. Michael's Hospital, Toronto (Canada)	The effect of high frequency oscillation on biological markers of lung injury	Observational	NCT00673517
Johns Hopkins University (USA)	Airway pressure release ventilation in acute lung injury	Randomized	NCT00750204
National Taiwan University Hospital (Taiwan)	Effect of mechanical ventilation strategy on lung injury in patients with less severe acute respiratory distress syndrome: targeted on RAGE	Non-randomized	NCT01301872
University of Milan (Italy)	The specific lung elastance in Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS) patients in supine and prone position	Non-randomized	NCT00568659
Larissa University Hospital (Greece)	Study of the influence of various tidal volumes on Exhaled Breath Condensate (EBC) in mechanically ventilated patients (TDEBC)	Randomized	NCT00910026
Beijing Chao Yang Hospital (China)	Noninvasive Positive Pressure Ventilation for early extubation of acute hypoxemic respiratory failure (NPPV)	Randomized	NCT01151501
University of Athens (Greece)	Study of a novel technique of mechanical ventilation in patients with severe acute respiratory failure (HFO-TGI-2)	Randomized	NCT00637507
Boston Medical Center (USA)	Biomarkers of lung injury with low tidal volume ventilation compared with airway pressure release ventilation	Randomized	NCT01038531
Federal University of Rio Grande do Sul (Brasil)	High tidal volume induces inflammation in normal lungs (Normallung)	Randomized	NCT00935896
Catholic University of the Sacred Heart (Italy)	Helmet CPAP vs Venturi O_2 to treat early ALI/ARDS (HelmetCPAP)	Randomized	NCT00342368
Centre hospitalier départemental Félix-Guyon (France)	Changes in refractory Acute Respiratory Distress Syndrome (ARDS) patients under high frequency oscillation-ventilation	Observational	NCT01167621
Canadian Critical Care Trials Group (Canada)	The oscillation for acute respiratory distress syndrome (ARDS) treated early trial - OSCILLATE	Randomized	ISRCTN87124254
National Heart, Lung, and Blood Institute (NHLBI) (USA)	Comparison of two methods of high frequency oscillatory ventilation in individuals with acute respiratory distress syndrome	Randomized	NCT00399581
Oxford University (UK)	Conventional positive pressure ventilation or High Frequency Oscillatory Ventilation (HFOV) for adults with acute respiratory distress sindrome – OSCAR: High Frequency OSCillation in ARDS	Randomized	ISRCTN10416500
Hôpital Ambroise-Paré (France)	Pulmonary and renal support during Acute Respiratory Distress Syndrome (PARSA)	Interventional	NCT01239966
University of Regensburg (Germany)	Extrapulmonary interventional ventilatory support in severe Acute Respiratory Distress Syndrome (ARDS) (Xtravent)	Randomized	NCT00538928

The source of the identification number is ClinicalTrials.gov (a registry of federally and privately supported clinical trials conducted in the United States and around the world) when the starting letters are ''NCT'', or Current Controlled Trials (the International Standard Randomised Controlled Trial Number Register when the initial letters are ''ISRCTN'').

Clinical definition of optimal PEEP

As discussed above, there is not significant clinical evidence showing what PEEP may be considered as optimal. One of the reasons is certainly the complexity of positive and negative clinical effects that PEEP may induce.

In fact, PEEP can either determine alveolar recruitment, with a consequent reduction of strain (change in size of the lungs during inflation, provided by the same tidal volume), or an excessive transpulmonary pressure, associated with increased stress on the lungs [58] and hemodynamic impairment. Hence,

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the evaluation in each patient with ALI or ARDS of the potentially recruitable areas of the lung seems crucial to identify optimal PEEP [59], which should be high enough to provide adequate oxygenation and lung recruitment, but low enough to prevent lung overdistension and hemodynamic failure.

One strategy to identify the potential for recruitment in an individual patient is the use of a short (30 min) trial of increased PEEP [30,54], monitoring gas exchange and compliance. If an increase in PEEP results in minimal improvement (or worsening) of PaO_2, an increase in dead space (increased $PaCO_2$) with stable minute ventilation and worsening compliance, then alveolar recruitment is minimal [58]. Conversely, if an increase in PEEP results in large increase in PaO_2, a decrease in $PaCO_2$ and improved compliance, it suggests significant recruitment. Some have suggested a decremental rather than an incremental PEEP trial [60,61].

However, the gold standard method to define lung recruitment is by CT scan. This strategy has been used by Caironi et al. to study 68 patients with ALI or ARDS, who underwent a CT based pressure–volume curves performed at 5, 15, and 45 cmH_2O of airway pressure [62]. The estimation of end-inspiratory and end-expiratory non-aerated portion of the lung at each given PEEP value allowed the calculation of the amount of opening and closing lung tissue, which is the tidal recruitment occurring at every breath. In patients with higher portion of recruitable lung, a higher PEEP significantly reduced the intra-tidal recruitment, whereas no difference was noticed in patients with a lower portion of recruitable lung. Interestingly, the alveolar strain increased similarly in the two groups with the increase of PEEP from 5 to 15 cmH_2O. Moreover, the amount of opening and closing lung tissue, and not alveolar strain, appeared to independently correlate with mortality. Therefore, as the authors suggested, a high PEEP strategy is certainly beneficial in ALI/ARDS patients with higher lung recruitability, because it prevents the tidal alveolar opening and closing and may reduce atelectrauma, which prevails, at least in these patients, over the effect of a higher PEEP-induced alveolar strain. Conversely, in patients with lower lung recruitability, a higher PEEP strategy would only cause detrimental effect, such as alveolar strain and hemodynamic impairment, without benefit.

An additional strategy to set optimal PEEP has been suggested by Talmor et al. [63]. They studied the use of an esophageal balloon to assess intrapleural pressure and titrate PEEP in order to maintain a constantly positive transpulmonary pressure [64]. The estimation of the intrapleural pressure by an esophageal balloon is not always feasible and requires physiological assumptions and corrections, which may lead to potential pitfalls [63]. Nonetheless, the results of this interesting clinical trial showed a significant improvement in oxygenation and a trend toward a lower mortality in the group of patients randomized to receive PEEP adjusted according to the esophageal pressure measurement as compared to patients treated according to the ARDS network strategy. Interestingly, the two groups differed for applied PEEP values, which were significantly higher in the esophageal balloon group, but not for the end inspiratory plateau pressure or the transpulmonary end inspiratory pressure, which was similar in the two groups, suggesting that higher PEEP may have prevented atelectrauma rather than alveolar overdistension.

New diagnostic tools

Measurement and monitoring of lung volumes and pressures during the different phases of the respiratory cycle would be extremely helpful to tailor treatment of patients with ALI or ARDS according to a physiology based strategy.

Recently, various diagnostic tools have been studied and developed to accomplish this purpose.

In particular, the electrical impedance tomography (EIT) [65], a real-time, noninvasive, radiation-free, bedside imaging technique that, similarly to the CT scan, can provide sectional tomograms of the lung [66], has shown very promising perspectives. Although currently still characterized by a not ideal spatial resolution [67], EIT provides both anatomical and functional breath by breath lung imaging, which can be used to assess and monitor ventilation and potentially also perfusion of the lungs [68,69]. High frequency and low amplitude electrical currents are delivered on the body surface, with the subsequent measurement of the resulting electrical potentials, which are converted into an anatomical distribution of impedance, which depends on the anatomical shape and the specific biochemical composition of the tissues [70].

The positron emission tomography can also provide anatomical and functional imaging of lung perfusion and ventilation, by measuring the concentration of a previously infused positron-emitting radioisotope within the body. Moreover, it can identify areas of inflammation, which may be of great help in better understanding the mechanisms of ALI and VILI.

Another promising diagnostic tool is the application of ultrasound to assess lung infiltrates and recruitment. A recent study demonstrated that it is possible with lung ultrasound to precisely estimated PEEP-induced lung recruitment [71]. However, this technique has major limitations in evaluating areas of alveolar overdistension. Future investigations will elucidate the full potentiality of this tool.

In addition to these promising imaging techniques, Grasso et al. [72] have recently proposed a dynamic stress index, calculated as the a dimensionless coefficient describing the shape of the pressure-time curve, during volume control ventilation with constant flow. In these conditions the ascending portion of the pressure-time profile predicts the respiratory system elastance during tidal inflation, being well described by the following equation: Paw = a bt + c. Where ''c'' is a constant, ''a'' is a scaling factor and ''b'' is the stress index. In particular, for b = 1 the slope of the curve is linear and hence the compliance is

constant throughout tidal inflation; for b < 1 the slope has a downward concavity due to the increase of compliance during tidal inflation, identifying mechanical stress induced by tidal recruitment of the lung; b > 1 indicates an upward concavity of the slope, due to the tidal decrease of compliance and therefore to hyperinflation-induced stress. Recently, the reliability of the stress index has been questioned in an experimental setting of unilateral pleural effusion [73]. In this extreme condition, despite absence of hyperinflation documented on CT scan, the stress index may exceed 1, suggesting that adequate clinical study with significant endpoints are needed to validate this tool. The stress index, if clinically established, may represent an optimal clinical tool at the bedside to prevent the occurrence of VILI.

Therapeutic perspectives

Along with novel diagnostic tools aimed at preventing or at least decreasing VILI, novel therapeutic strategies for ALI/ARDS have been proposed as adjunctive to the standard of care or as a alternative treatment, especially in those patients whom, despite the use of protective ventilation, lung injury may still persist or progress.

Recruitment maneuvers

A recruitment maneuver (RM) is a transient increase in transpulmonary pressure aiming at the reopening of collapsed alveoli or lung areas with persistent collapse and repetitive opening and closing, potentially resulting in atelectrauma [29,74]. Clear evidences have shown that RM increases the amount of aerated lung tissue, thus improving gas exchange [75–78]. However, RM may also cause an excessive stress and strain in regions of healthy lungs, which paradoxically may contribute to VILI. RM can be performed with a number of different techniques [58]. A common way to recruit the lung is to do a sustained high-pressure inflation using pressure of 30 to 50 cmH$_2$O for 20 to 40 seconds [77]. Pressure-controlled breaths can be applied in addition to the sustained high pressure [79,80]. Another approach is to use periodic sighs by setting three consecutive sighs per minute with the tidal volume reaching a plateau pressure of 45 cmH$_2$O in volume control mode [81]. An extended sigh corresponding to the alveolar pressure of total lung capacity (30–35 cmH$_2$O) for a prolonged time may also be considered as RM. For the extended sigh, from the baseline ventilator setting, PEEP is increased stepwise by 5 cmH$_2$O every 30 seconds with a concomitant stepwise decrease of tidal volume by 2 mL/kg. At tidal volume of 2 mL/kg and PEEP of 25 cmH$_2$O, ventilation mode is switched to CPAP of 30 cmH$_2$O for 30 seconds, after which the baseline setting is resumed following the reverse sequence of the inflating procedure. This extended sigh is given twice with 1 min of baseline ventilation between [82]. Another method applies an intermittent increase in PEEP from baseline to a predefined higher level for the duration of two consecutive

ventilatory [76]. Finally, a pressure-controlled ventilation of 10 to 15 cmH$_2$O with PEEP of 25 to 30 cmH$_2$O to reach a peak inspiratory pressure of 40 to 45 cmH$_2$O for 2 minutes has also been used as RM [79].

Currently, it has not been established whether RM are providing significant benefit in terms of meaningful clinical outcome, beside a transient improvement in gas exchange, and which type of RM is potentially more efficient [30,83–85]. Many patients require increased sedation, paralysis, or both during the application of a RM. In addition, the increased airway pressure during recruitment maneuvers sometimes results in transient adverse events, as hypotension (12%) and desaturation (8%). However, serious adverse events related to RMs, such as barotrauma (e.g., new pneumothorax) (1%) and arrhythmia (1%) remain rare [29]. In clinical practice, if the application of a RM results in an important improvement in oxygenation, higher levels of PEEP should be used to maintain recruitment [58].

Prone positioning

Patients with ARDS maintained in the supine position tend to develop atelectasis in the dependent regions of the lung and shunting through these areas. Placing a patient in the prone position is an adjunctive strategy that has been used to improve oxygenation in patients with severe ARDS particularly those with refractory hypoxemia. With the patient in the prone position, the shift in gravitational forces reduces atelectasis and minimizes compression of lung parenchyma by the heart and mediastinal structures, resulting in recruitment of dorsal lung segments, improved ventilation-perfusion matching, and more homogeneous distribution of ventilation [46,86]. Currently there are two methods of providing prone positioning ventilation. Traditionally the patient is turned from supine to prone position on a standard ICU bed, and this requires from three to six trained people to ensure patient safety. Another method involves the use of a proprietary rotational bed (Rotoprone; KCI Medical Products, San Antonio, Texas) that rotates the patient. However, regardless of the method used, the process of placing a critically ill patient in the prone position can be labor intensive and increases the risk of accidental removal of endotracheal tube, other drains, or catheters and development of pressure sores [87].

Currently, multicenter randomized trials [88–91] and systematic reviews/meta analysis [92–96] on prone positioning have demonstrated improvement in oxygenation, but have failed to demonstrate a survival benefit. However, the results of one of the first randomized trials [88] suggested that in the subgroup of ARDS patients with the most severe hypoxemia survival was better in the prone than in the supine position. Based on these findings, a new recently published randomized trial [91] was performed to detect the potential survival benefit of prone positioning in this more severe patient population with ARDS, while avoiding known limitations of previous trials. Thus,

patients with ARDS were stratified a priori into a subgroup of patients with moderate hypoxemia and subgroup of patients with severe hypoxemia. A lung protective mechanical ventilation strategy was implemented in both the supine and prone groups, daily prone positioning was applied early (within 72 hours) and prolonged for up to 20 hours per day. However, despite these measures, also this study failed to demonstrate either 28-day or 6-month survival benefit between the prone and the supine groups, although there was a statistically not-significant 10% difference in mortality favoring the prone patients in the severe hypoxemia subgroup (28-day mortality: 37.8% in the prone and 46.1% in the supine group, relative risk of death 0.87; 95% CI, 0.66–1.14; P = 0.31; 6-month mortality: 52.7% and 63.2%, respectively, relative risk of death 0.78; 95% CI, 0.53–1.14; P = 0.19). Of note, the proportion of patients with complications was significantly higher in the prone group.

In a recent meta-analysis by Sud et al. [97], the authors evaluated the effect of prone positioning among all patients with ALI and in a predefined subset of patients with severe hypoxemia (i.e. PaO_2/FiO_2 ratio $<$ 100 mmHg). In this last subset of patients, this meta-analysis found a significantly improved survival benefit (relative risk of death 0.84; 95% CI, 0.74–0.96; P = 0,01), but the complications such as pressure ulcers, endotracheal tube obstruction, unplanned extubation, loss of central venous access, chest tube dislodgement, and increased use of sedation persisted [97].

Finally, Gattinoni et al. [98] have recently displayed Kaplan-Meier estimates of survival rates of patients enrolled in the four large RCTs investigating the effects of prone positioning. In this paper, patients from the entire population obtained were retrospectively classified as either moderately hypoxemic (i.e., PaO_2/FiO_2 ratio 200–100 mmHg) or severely hypoxemic (i.e., PaO_2/FiO_2 ratio $<$ 100 mmHg). The entire pooled population and the moderately hypoxemic patients treated with prone positioning had similar outcomes as those treated with supine positioning. In contrast, when severely hypoxemic patients from the pooled population were considered, prone positioning was associated with a significantly improved survival benefit, with an absolute mortality reduction at the last follow-up of approximately 10% (ranging between 6% and 21% in the different trials) [59].

Therefore, given the available data and the associated risks, the use of prone positioning should not be routinely used for all patients, and only considered as a rescue strategy in patients with ARDS and severe refractory hypoxemia [46,97,98].

High frequency ventilation

An approach to mechanical ventilation that is considered theoretically ideal in minimizing VILI in patients with ARDS is high frequency ventilation, defined as any application of mechanical ventilation with a respiratory rate of $>$ 100 breaths/min [58]. This can be achieved with a small tidal volume and rapid respiratory rate with conventional mechanical ventilation, high

frequency percussive (HFP) ventilation [99], high frequency jet ventilation, or high frequency oscillatory (HFO) ventilation [100], which currently is the form of high frequency ventilation most widely used in adult critical care. During HFO, very small tidal volumes (less than anatomic dead space) are delivered at high frequency (typically in the range of 300 to 900 breaths/min). This modality allows the use of a relatively constant higher mean pressure to recruit the lung and maintain the alveoli open, while simultaneously avoiding tidal hyperinflation [101]. The gas exchange in HFO occurs through unconventional (non-convective) flow mechanisms [102]. The mean airway pressure and FiO_2 are the primary determinants of oxygenation, whereas the pressure amplitude of oscillation and the respiratory frequency are the determinants of CO_2 elimination [103]. HFO has been combined with other strategies, such as recruitment maneuvers [104], inhaled nitric oxide [105], and prone positioning [106]. Most of the evidence for HFO has been from small observational studies, often in the setting of refractory hypoxemia. These studies have shown that HFO is technically feasible and generally tolerated, resulting in improvements in oxygenation [107–110]. Complications reported with HFO are relatively infrequent and include barotrauma [107,110,111], hemodynamic compromise [108,110], mucus inspissations resulting in endotracheal tube occlusion or refractory hypercapnia, and increased use of sedation or neuromuscular blocking agents (NMBA) [107,108,111,112].

There have been only few randomized clinical trials on HFO in adult ARDS patients [111,113]. In the largest multicenter trial, Derdak et al. [111] randomized 148 patients with ALI/ARDS to receive either HFO or conventional ventilation (pressure control ventilation). The HFO group showed an early improvement in the PaO_2/FiO_2 ratio, but this was not sustained beyond 24 h. The same group also had a non-significant trend toward a lower 30-day mortality rate (37% vs 52%; P = 0.102). Most studies of HFO have employed frequencies of 6 Hz (respiratory rate = 360 oscillations/minute) or less. In theory, higher frequencies (e.g., up to 15 Hz) would result in smaller tidal volumes and potentially less VILI. Fessler et al. recently published a case series of 30 patients with ARDS and refractory hypoxemia treated with HFO; their strategy was to use the smallest tidal volume possible at the highest frequency that allowed acceptable CO_2 clearance [114]. In 25 out of 30 patients, adequate gas exchange was maintained at frequencies greater than 6 Hz. In these patients the mean maximal frequency was 9.9 ± 2.1 Hz, at an oscillation pressure amplitude of 81 ± 11 cmH$_2$O. Survival to hospital discharge was 37%. Recently, Sud et al. reported a meta-analysis of the effect of HFO in patients with ALI/ARDS [115]. The analysis from six trials conducted in adults or children (365 patients) found that HFO significantly reduced mortality (relative risk 0.77, 95% CI 0.61–0.98, P = 0.04) compared to conventional mechanical ventilation. A limitation of this meta-analysis is the relatively small number and size of the studies

and their qualitative heterogeneity, including the lack of pressure limited ventilation and volume limited ventilation in a large number of control patients [116]. However, in a post hoc analysis that excluded trials that allowed tidal volumes $\geq$ 8 mL/kg of PBW in the control group, there was a trend toward lower mortality among patients who received HFO (RR 0.67, 95% CI 0.44–1.03). Hopefully, clear evidence on the effectiveness of HFO as treatment in ARDS will be provided by the results of two ongoing randomized multicenter controlled clinical trials: the Oscillation for ARDS Treated Early (OSCILLATE) Trial (International Standard Randomised Controlled Trial Number Register identification: ISRCTN87124254; planned n = 1200), and the Conventional Positive Pressure Ventilation or High Frequency Oscillatory Ventilation for Adults with ARDS (OSCAR) Trial (ISRCTN10416500; planned n = 802).

Neurally adjusted ventilatory assist

The neurally adjusted ventilatory assist (NAVA) is a recently developed mechanical ventilation strategy, representing a promising advancement in the field of artificial ventilation. NAVA delivers respiratory assistance in synchrony and proportionally breath-to-breath to the diaphragmatic electrical activity, which is constantly measured by a specific array of electrodes attached to a nasogastric tube. NAVA was shown to be as effective as the low tidal volume strategy in attenuating VILI in an experimental animal model of ALI [117]. However, more data are needed to confirm its efficacy in supporting patients with severe hypoxemic respiratory failure.

Noninvasive mechanical ventilation

Noninvasive mechanical ventilation (NIV) has been shown to be effective in improving survival in certain forms of acute respiratory failure, such as exacerbation of chronic obstructive pulmonary disease [118]. However, its benefit remains unclear in patients with acute hypoxemic respiratory failure. Several controlled trials failed to show an improvement in survival in patients treated with NIV as opposed to invasive mechanical ventilation. Moreover, although clinical trials have suggested that patients with acute hypoxemic respiratory failure treated with NIV are less likely to require endotracheal intubation, this beneficial effect has not been confirmed in other large clinical investigations [119]. Therefore, current evidence does not support the routine application of NIV for ARDS. However, a transient attempt of NIV may be applied in these patients as first line treatment but only in specific centers with proven expertise.

Extracorporeal CO_2 Removal

Protective mechanical ventilation is based on delivery of low tidal volume and low pressure. However, as mentioned above, a safe tidal volume or pressure threshold could not be identified for all patients. Ideally, injured lungs should be ''rested'' without undergoing any mechanical stress or strain, providing enough time for the lung to completely heal [120]. Toward this end, a conspicuous research effort has been carried out to investigate the efficacy of different strategies of extracorporeal circulation to support respiratory function.

The first successful case of extracorporeal membrane oxygenation (ECMO) to support a patient with acute respiratory failure was reported by Hill et al. in 1972 [121]. This case was followed by a randomized trial, which was stopped in advance after recruitment of 90 patients for futility and significantly discouraged the research on this field [122].

However, in the 1980s Gattinoni et al. studied in patients with severe ARDS the use of a veno-venous ECMO to efficiently remove CO_2, while providing oxygenation using continuous O_2 flow at the airway opening and high levels of PEEP [120]. The results showed a mortality rate of approximately 50%, which was significantly lower than expected, but the study did not contemplate a control group. Furthermore, a high rate of complications, such as major bleeding and blood loss in the circuit, was reported. Also Morris and colleagues performed a randomized clinical trial comparing pressure controlled inverse-ratio ventilation with veno-venous ECMO in patients with ARDS, but they did not find significant differences between groups [123]. The results of these trials, the rate of complications and the amount of resources needed to apply ECMO have largely limited for a significant period of time its clinical application especially for patients with acute respiratory failure.

More recently, the technology development has provided new extracorporeal circuits with heparin-bonded cannulae requiring less anticoagulation, rotary pumps, and small efficient long-lasting oxygenators. This significant advancement has led to a renewed clinical interest on ECMO as treatment for patients with severe ARDS. In fact, two large clinical trials have been published in the year 2009, providing very interesting results. The Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigators reported the results of an observational trial on 68 patients with H1N1 influenza-associated ARDS and treated with ECMO, during the pandemic of 2009 [124]. These patients, before ECMO, were diagnosed with severe ARDS, characterized by a PaO_2/FiO_2 ratio of 56 (48–63), PEEP of 18 (15–20) cmH$_2$O, and an ALI score of 3.8 (3.5–4.0), despite treatment with advanced measures of invasive mechanical ventilation. The ICU mortality rate was 71% (95% confidence interval, 60–82%), in fact 48 out of 68 patients survived ICU discharge and 32 survived hospital discharge, of whom 31 were able to walk. Major bleeding was the cause of death in 10 patients, of whom six had intracranial hemorrhage.

A second multicentre United Kingdom-based trial, the so called CESAR trial [125], has randomized 180 patients with severe ARDS to be considered for ECMO, and therefore transferred to a single ECMO center, or to continue with the conventional ventilation strategy. Ninety patients were randomized to the group to be considered for ECMO. Although only 75% of these patients (68 out of 90) actually received ECMO, overall this

group had a significantly higher survival (63%) at 6 months without disability as compared to the control group receiving conventional treatment (47%, relative risk 0.69; 95% CI 0.05–0.97, P = 0.03). Also in this trial the rate of complications related to the application of ECMO was low. Interestingly, the benefit of being randomized in the ECMO group disappeared if the patients allocated in this group, but not treated with ECMO, were removed and not considered in the statistical analysis. Hence, although the study may not be conclusive on the clinical efficacy of ECMO, it strongly suggests that the allocation of patients with severe ARDS in a centralized facility with proven expertise may be a crucial issue in the management of this clinical condition.

In addition to ECMO, other less invasive strategies of extracorporeal assist have been developed and studied on ARDS patients with the aim of enhancing the protection of the lung during mechanical ventilation. In particular, a pumpless arteriovenous extracorporeal lung assist (interventional Lung Assist: iLA Nova-Lung GmbH, Hechingen, Germany) very efficient in removing carbon dioxide, has been proposed for the treatment of patients with critical ARDS to prevent hypercapnia [126]. In two different clinical studies this technique allowed the reduction of tidal volume to below 4 mL/kg of PBW [127,128]. Although very promising, this strategy carries major issues, such as the need to rely on the arteriovenous pressure gradient to generate blood flow, which thus depends only on the hemodynamic status of the patient, as well as the need of arterial cannulation that can induce lower limb ischemia. Another minimally invasive extracorporeal CO_2 removal device (ECCO2-R, Decap®, Hemodec, Salerno, Italy) consisting of a pump-driven (0–500 mL/min) veno-venous hemofiltration system equipped with a membrane lung (0.33 m^2) within a standard system for renal replacement therapy has been applied in patients with severe ARDS (25 < PPLAT < 28 cmH$_2$O). The main features of this system as opposed to the ECMO or iLA NovaLung are a lower blood flow (5–10% of cardiac output), the use of smaller (14-French) double-lumen catheters, and a relatively small infusion rate of heparin (3–19 IU/kg). This novel approach, by maintaining a normal PaCO$_2$, allowed a significant reduction in tidal volume from 6.3 ± 0.2 to 4.2 ± 0.2 mL/kg of PBW, which resulted in a significant decrease of lung hyperinflation on CT scan and a significant reduction of inflammatory mediators in the lung [129].

Future randomized clinical trials will further test these extracorporeal treatments to better identify their specific clinical indication and efficacy.

Neuromuscular blocking agents

From 25 to 55% of patients with ALI/ARDS receive NMBA, a prevalence that increases further with use of non-conventional modes of ventilation, as mentioned above [30,31,112,130,131]. Current guidelines indicate that NMBA are appropriate only to improve patient–ventilator synchrony and oxygenation, especially if gas-exchange is severely impaired [132], but do not encourage a routinely use of NMBA in patients with ARDS.

However, a recent multicenter, double-blind randomized clinical trial has showed that early administration of a 48-hour infusion of cisatracurium in patients with severe ARDS improves the adjusted 90-day survival rate (hazard ratio for death 0.68 after adjustment for baseline PaO$_2$/FiO$_2$ ratio, plateau pressure and Simplified Acute Physiology II score; 95% CI 0.48–0.98), increases the number of ventilator free days, and decreases the incidence of barotrauma [133]. Interestingly, the beneficial effect of cisatracurium on the survival rate seemed to higher for patients with worst oxygenation (PaO$_2$/FiO$_2$ less than 120 mmHg). The mechanisms underlying this beneficial effect of NMBA remain still unclear [134]. A possible reason of the benefit involves a decrease in lung or systemic inflammation, although other potent anti-inflammatory drugs, such as steroids, failed to show clear benefit in ARDS [135]. NMBA decreases the total body oxygen consumption, thereby improving oxygen delivery and consequentially potentially ventilation-perfusion relationships [136]. However, improved oxygenation is unlikely to be the major explanation for the positive results of this clinical trial, since gas-exchange measurements were essentially the same in the two groups during cisatracurium administration. Finally, NMBA may decrease the risk of VILI by reducing patient-ventilator asynchrony, improving the accurate adjustment of tidal volume and pressure levels, and allowing a better setting of PEEP [134]. In fact, in this study the control group had a significant higher incidence of barotrauma and pneumotorax.

However, a major concern of using NMBA remains the induced muscle weakness, which may affect patient short and long term prognosis. In their study, Papazian et al. found that study muscle weakness was not increased significantly by the use of the cisatracurium.

Nitric oxide

Nitric oxide is a potent vasodilator, which, delivered by inhalation, becomes available to the vessels in the ventilated areas of the lung, thus enhancing ventilation and perfusion matching with consequent improvement in oxygenation. These effects have been considered a strong rationale to perform several clinical trials to investigate the potential therapeutic role of inhaled NO in patients with ARDS. Unfortunately, beyond an improvement in oxygenation none of the trial showed a significant improvement in survival [46]. Therefore, inhaled NO is not currently suggested for routine treatment in ARDS patients, but is occasionally considered as adjunctive treatment in rescue conditions.

Lung transplantation

Lung transplantation is an effective procedure that prolongs survival and improves quality of life in patients with end stage lung failure, usually caused by progressive chronic lung

diseases, such as cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis. The indication to lung transplantation needs careful consideration, as the number of available donor lung is low and the survival rate of transplanted patients at five years is still about 50% [137].

Therefore, lung transplantation is infrequently considered as definitive treatment for acute respiratory failure, such as ARDS. In fact, these patients often present significant co-morbidities or MOF, which preclude their suitability for transplantation. Moreover, the issues of prognosis definition, time for candidate evaluation and consent acquisition are challenged by the acuity of the clinical conditions.

However, the possibility of applying measures of prolonged life support, such as ECMO, has overcome some of these issues. Hence, patients with acute single organ failure, i.e. lung, with no meaningful prospective of any recovery and no pre-existing co-morbidities, may be considered, on an individualized basis, for lung transplantation. There have been several case reports of patients receiving lung transplant while supported by invasive mechanical ventilation, ECMO, or other means of respiratory support, as a bridge strategy to a more definitive treatment [138–140].

Prospectively, a significant increase in the number of donor lungs, which may be achieved through various strategies [141,142], would further broaden the indication to lung transplantation, including patients with ARDS refractory to other rescue therapies.

Conclusions and implications

Acute respiratory failure, especially in the more severe forms of ALI and ARDS, remains a challenging medical problem in the intensive care setting. In the recent past, there have been made exciting advances, which have been summarized in this review. It is increasingly likely that the integration of physiological, technological and clinical discoveries will continue to improve the outcome of patients with acute respiratory failure in the future.

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