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REVIEW ARTICLE

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Future directions of lung-protective ventilation strategies in acute respiratory distress syndrome

Taiki Hoshino | **Takeshi Yoshida**

The Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Suita, Japan

Correspondence
Takeshi Yoshida, The Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, 2-15 Yamadaoka, Suita, Osaka 565-0871, Japan.
Email: takeshiyoshida@hp-icu.med.osaka-u.ac.jp

Abstract

Acute respiratory distress syndrome (ARDS) is characterized by the heterogeneous distribution of lung aeration along a gravitational direction due to increased lung density. Therefore, the lung available for ventilation is usually limited to ventral, nondependent lung regions and has been called the "baby" lung. In ARDS, ventilator-induced lung injury is known to occur in nondependent "baby" lungs, as ventilation is shifted to ventral, nondependent lung regions, increasing stress and strain. To protect this nondependent "baby" lung, the clinician targets and limits global parameters such as tidal volume and plateau pressure. In addition, positive end-expiratory pressure (PEEP) is used to prevent dorsal, dependent atelectasis and, if successful, increases the size of the baby lung and lessens its susceptibility to injury from inspiratory stretch. Although many clinical trials have been performed in patients with ARDS over the last two decades, there are few successfully showing benefits on mortality (ie, prone positioning and neuromuscular blocking agents). These disappointing results contrast with other medical disciplines, especially in oncology, where the heterogeneity of diseases is recognized widely and precision medicine has been promoted. Thus, lung-protective ventilation strategies need to take an innovative approach that accounts for the heterogeneity of injured lungs. This article summarizes ventilator-induced lung injury and ARDS and discusses how to implement precision medicine in the field of ARDS. Potentially useful methods to individualize PEEP with esophageal balloon manometry, lung recruitability, and electrical impedance tomography were discussed.

KEYWORDS

ARDS, esophageal balloon, mechanical ventilation, PEEP, precision medicine

VENTILATOR-INDUCED LUNG INJURY AND LUNG-PROTECTIVE VENTILATION STRATEGY

In acute respiratory distress syndrome (ARDS), inflammation increases lung density, causing a heterogeneous distribution of lung aeration along the gravitational direction.[1] In the supine position, the dorsal, dependent lung regions are likely to collapse due to increased lung density, and thus, the lung available for ventilation is usually limited to the ventral, nondependent lung regions, similar to the lung volume of a 5- to 6-year-old child.[1] It is known as the "baby" lung.[1] Recent studies using fluorodeoxyglucose–positron emission tomography have indicated that actively inflamed areas are observed in ventilated lung regions, namely, normal lung regions continuously exposed to ventilation, rather than in nonventilated areas, such as lung collapse.[2–4] Therefore, minimizing inflammation in the normal "baby" lung regions is the primary goal of lung-protective ventilation strategies.

The Acute Respiratory Distress Syndrome Network trial published in 2000 (ARMA) was a landmark clinical trial investigating the impacts of lung-protective ventilation

strategies in patients with acute lung injury (ALI) and ARDS.[5] The study aimed to determine whether lower tidal volumes and lower plateau pressure could improve outcomes compared with traditional ventilation strategies. The study enrolled 861 patients with ALI or ARDS and randomized them into two groups. One group received traditional ventilation with tidal volumes of 12 mL/kg of predicted body weight and a plateau pressure of 50 cmH_2O or less, while the lung-protective ventilation group received ventilation with lower tidal volumes of 6 mL/kg of predicted body weight and a plateau pressure of 30 cmH_2O or less. The results of the ARMA study showed a significant reduction in mortality among patients receiving lower tidal volumes. The lung-protective ventilation group receiving a lower tidal volume and lower plateau pressure had a mortality rate of 31.0% compared with 39.8% in the traditional ventilation group.

To protect the nondependent "baby" lung, clinicians adopt a strategic approach by targeting and restricting global parameters, including tidal volume and plateau pressure. This practice stems from findings in the ARMA trial, which highlighted the advantages of using a lung-protective ventilation strategy in cases of ARDS. The objective is to capitalize on the benefits associated with lower tidal volume and plateau pressure, with the intention of reducing the vulnerability of the ventral "baby" lung to injury caused by inspiratory stretch.[6]

MANY TRIALS FAILED TO SHOW BENEFITS IN ARDS

The mortality rate of patients with ARDS, however, has remained high over the last two decades, despite lung-protective ventilation.[7] An epidemiologic study published in 2005 by Rubenfeld et al[8] found that in 1113 patients who underwent mechanical ventilation and met the criteria for ALI, the in-hospital mortality rate was 38.5%. Approximately 10 years later, another epidemiologic study conducted by Bellani et al[7] investigated the mortality rates for patients with ARDS in 50 countries worldwide (LUNG SAFE study). During the winter of 2014, out of 29,144 intensive care unit admissions, 10.4% had ARDS. Among them, 2377 patients needed mechanical ventilation due to respiratory failure. The LUNG SAFE study found that the mortality rates for mild, moderate, and severe ARDS were 34.9%, 40.3%, and 46.1%, respectively (Figure 1).

Many clinical trials in supportive care have been performed since the ARMA trial, but only two have successfully been shown to improve mortality in patients with ARDS.[9] First, systemic use of neuromuscular blocking agents in conjunction with lung-protective ventilation strategies including a lower positive end-expiratory pressure (PEEP)–fraction of inspired oxygen (FiO_2) table reduced the incidence of barotrauma and mortality in patients with severe ARDS.[10] This is probably because the silencing of respiratory muscles prevents additional lung stretch imposed by spontaneous breathing activity and prevents patient–ventilator asynchrony.[11] Of note, the re-evaluation of the systemic early neuromuscular blockade (ROSE) trial found no benefits of routine use of neuromuscular blocking agents in ARDS when applying a higher PEEP–FiO_2 strategy.[12] Higher PEEP may render spontaneous effort less injurious, thereby confounding the impact of the intervention.[13] Second, the prone position in conjunction with the lung-protective ventilation strategy also reduced mortality in patients with severe ARDS.[14] The prone position helps to increase the end-expiratory lung volume, probably depending on lung recruitability, the shape of the chest wall, the presence of abdominal hypertension, and the presence of support.[15] Thus, the prone position reduces the heterogeneity of lung aeration in ARDS. Regarding pharmacological therapies, more than 20 clinical trials have been performed thus far, for example, using nitric oxide, surfactant, beta2 agonist, simvastatin, sivelestat, and omega 3 supplementation, but all of them have failed to show the benefits of improving mortality in patients with ARDS.[9] Of note, all pharmacological therapies successfully passed preclinical studies in experimental models of lung injury and even phase I/II clinical trials. These disappointing results contrast with other medical disciplines, especially in oncology, where ≈10% of

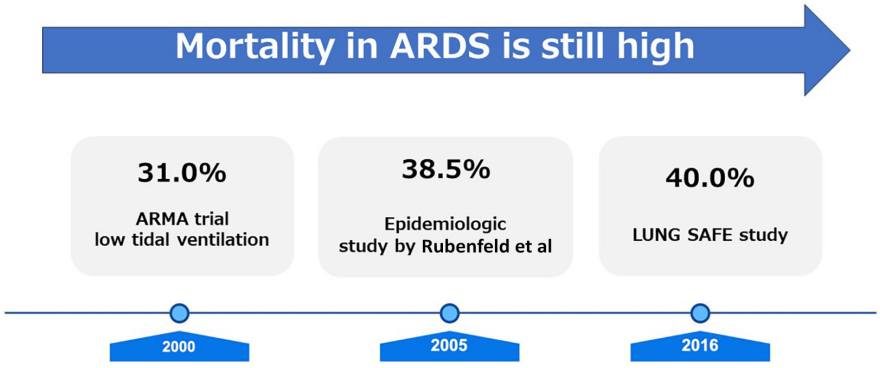

FIGURE 1 Epidemiology of ARDS. Over the last two decades since the ARMA trial, in-hospital mortality in patients with ARDS has not decreased dramatically. ARDS, acute respiratory distress syndrome.

drugs found to be beneficial and safe in preclinical investigations are implemented in daily practice and included in recommendations in the guidelines.[16] Although the anti-inflammatory effect of corticosteroids might improve the prognosis of ARDS, many studies have failed to show their benefits thus far, and thus, the efficacy of corticosteroids in ARDS remains controversial. A recent clinical trial showed that early administration of dexamethasone could reduce the duration of mechanical ventilation and overall mortality in patients with moderate-to-severe ARDS. Of note, enrolled patients were ventilated with lung-protective mechanical ventilation, different from previous studies on corticosteroids.[17] Of course, more substantial evidence will be necessary to confirm the efficacy of corticosteroids in ARDS.

The definition of ARDS is excellent for screening but poor for diagnosis.[18] This is because ARDS is a biologically and physiologically heterogeneous syndrome but not a disease with a single mechanism that is responsive to singular intervention.[18] Underlying diseases, risk factors, severity, and causes of ARDS will lead to substantial differences in pathophysiology and, of course, response to specific interventions. Thus, the probability of success in ARDS clinical trials can be enhanced by reducing such heterogeneity among enrolled patients. Trials of neuromuscular blocking agents[10] and the prone position[14] are good examples that could show the value of reducing heterogeneity among enrolled patients.

These two clinical trials focused on patients with more severe ARDS and reduced the heterogeneity among enrolled patients. Initially, clinical trials on the prone position included an unselected population of patients with ARDS from the perspective of severity and failed to improve mortality.[19–22] Gattinoni et al[23] performed a *post hoc* analysis of four major clinical trials on the prone position and found that its benefit on mortality was limited to patients with severe ARDS (ie, arterial oxygen pressure $[PaO_2]/FiO_2$ <150 mm Hg). When heterogeneity was reduced by enrolling patients with only severe ARDS, the PROSEVA trial successfully showed improved mortality in ARDS.[14] In this trial, 466 patients with severe ARDS were randomized to early (<36 h after intubation), lengthy (16 h per day), and intermittent prone position or to a standard supine position. The prone position led to decreased 28-day mortality (16.0% vs 32.8%) and 90-day mortality (23.6% vs 41.0%). The ACURASYS trial has shown the same direction.[10] Systemic use of neuromuscular blocking agents was shown to improve mortality in moderate-to-severe ARDS, but the greatest benefit was shown in patients with PaO_2/FiO_2 less than 120 mm Hg. A recent study reported that machine learning classifier models were helpful in identifying the ARDS phenotype of hyperinflammatory or hypoinflammatory conditions and thus reduced the heterogeneity of ARDS.[24] Of note, the phenotypes have widely divergent clinical outcomes, and differential treatment responses have been identified for PEEP,[25] fluid therapy,[26] and simvastatin.[27]

To further decrease mortality in ARDS, ventilatory strategies need to be tailored by detecting each subgroup/phenotype response to specific interventions.

PERSONALIZED VENTILATORY STRATEGY FOR ARDS

Individualizing tidal volume

In patients with ARDS, the lung parenchyma available for ventilation is reduced, and the size of nondependent "baby" lung regions is variable among patients.[28] As tidal volume is scaled to body size (predicted body weight is based on "height" and "gender"),[5] a tidal volume of 6 mL/kg of predicted body weight does not always help to reduce stress and strain. The smaller the size of the "baby" lung available for ventilation, the greater the amount of cyclic parenchymal deformation, even if the tidal volume is reduced to 6 mL/kg of predicted body weight. The physiological parameter that correlates with the size of the lung available for ventilation is known to be respiratory system compliance (Crs). Amato et al[28] proposed that tidal volume should be individualized (normalized) by each size of lung available for ventilation (ie, Crs), and that using the ratio as an index indicating the "functional" size of the lung would provide a better predictor of outcomes in patients with ARDS than tidal volume alone. This ratio, termed driving pressure (tidal volume divided by Crs), was most strongly related to survival, which was found by analyzing data from nine previous clinical trials. This concept was confirmed in several clinical studies by showing that driving pressure was associated with hospital mortality.[29,30]

Individualizing PEEP

Theoretically, PEEP is used to prevent dorsal (dependent) atelectasis and, if successful, increases the size of the baby lung and lessens its susceptibility to injury from inspiratory stretch. There is an experience-based method for determining PEEP corresponding to pulmonary oxygenation capacity (ie, the PEEP–FiO_2 table).[5] Although a meta-analysis revealed that higher PEEP was associated with better outcomes in severe ARDS,[31] no optimal method to set PEEP has been shown thus far. This is probably because the response to PEEP (ie, lung recruitability) is variable among patients with ARDS.[32] Several methods to individualize PEEP are presented here.

Esophageal balloon manometry

The global parameter of airway pressure (eg, PEEP) reflects distension of the lung and chest wall.[33,34] Airway pressure applied to the respiratory system degenerates into two components: distending chest wall (pleural pressure) and

distending lung (transpulmonary pressure).[33,34] The proportion of lung distending pressure to airway pressure is variable among patients with ARDS, depending on obesity and so on. Esophageal balloon manometry is the only clinically available technique to separate airway pressure into pleural pressure and transpulmonary pressure.[33] Therefore, esophageal balloon manometry has the potential to optimize PEEP by maintaining sufficient lung distending pressure rather than targeting pressures applied to the whole respiratory system. To prevent atelectasis, it has been proposed to adjust PEEP such that expiratory transpulmonary "distending" pressure is slightly positive, and this is assumed to ensure that the lung (if recruitable) is maintained open (Figure 2).[35]

A recent study has shown that absolute esophageal pressure is not affected by the weight of the heart or mediastinum and accurately reflects the local pleural pressure where the esophageal balloon is located, that is, the mid-to-dorsal lung, which is usually affected by lung collapse.[34] Thus, it is reasonable to set the PEEP such that the expiratory transpulmonary pressure calculated from the absolute esophageal pressure is greater than 0 to prevent alveolar collapse. Talmor et al[35] conducted a single-center randomized controlled trial based on the hypothesis that PEEP with an expiratory transpulmonary pressure greater than or equal to 0 is necessary to prevent alveolar collapse. In this trial of EPVent,[35] 61 patients with ARDS were randomized to PEEP adjusted according to measurements of esophageal pressure or according to the Acute Respiratory Distress Syndrome Network standard-of-care recommendations, that is, low PEEP–FiO_2 table. The results showed that oxygenation and respiratory compliance improved more in the esophageal pressure-guided group. In the EPVent-2 trial,[36] the esophageal pressure-guided group showed no improvement in mortality and no increase in ventilator-free days. *Post hoc* reanalysis of the EPVent-2 trial found that, independent of baseline severity or treatment group, mortality was lowest when expiratory transpulmonary pressure was close to 0 cm H_2O (vs more positive or negative value).[37] A recent observational study found the effectiveness of esophageal balloon manometry to set the PEEP.[30] The maintenance of expiratory transpulmonary pressure greater than 0 cmH_2O was associated with better 60-day mortality in patients with obesity (body mass index > 30 kg/m^2).[30]

Recruitability

In 2006, Gattinoni et al[32] conducted a computed tomography study to investigate the relationship between the percentage of potentially recruitable lungs and the physiological effects of PEEP. In ARDS, the percentage of potentially recruitable lungs was extremely variable among patients and was strongly associated with the response to PEEP. Such heterogeneity can partially explain why none of the PEEP clinical trials thus far have improved outcomes in patients with ARDS. Thus, an effort should be made to identify the subgroup likely to recruit in response to higher PEEP.

Recently, the recruitment-to-inflation ratio (R/I ratio) has been developed as a simple bedside technique to identify patients who have the potential for lung recruitment.[38] The R/I ratio is calculated with expiratory tidal volume measured at the time of releasing PEEP 15–5 cmH_2O (or airway opening pressure, either of which was higher). The difference in expired tidal volume between high and low PEEP is the sum of the volume recruited by PEEP and the volume distributed in the already aerated lung. This ratio indicates the ratio of compliance of the recruited lung to the compliance of the already aerated lung. According to previous studies, an R/I ratio greater than 0.5–0.7 indicates good recruitability.[38–40]

Taenaka et al[40] examined the recruitability of 43 patients with coronavirus disease 2019 (COVID-19)–associated ARDS using the R/I ratio both in supine and in prone positions and then proposed the optimal ventilatory strategy based on

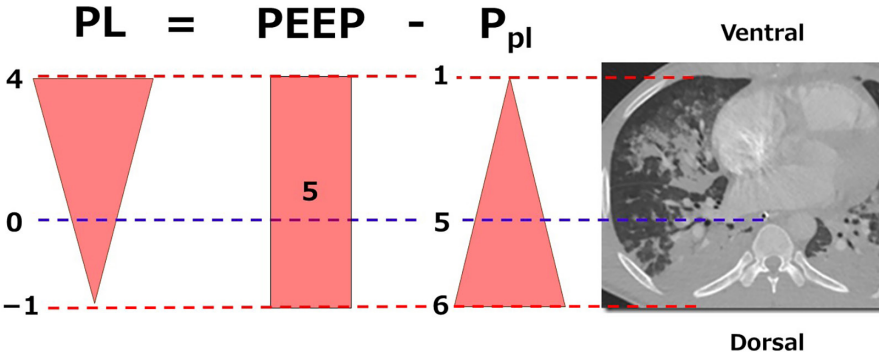

FIGURE 2 Lung region and pleural pressure. As inflammation increases lung density in ARDS, pleural pressure is greater in more dorsal lung regions by gravity, causing a large vertical gradient of pleural pressure in a gravitational axis (the closed triangle indicates less pleural pressure in ventral, more pleural pressure in dorsal). Hence, transpulmonary pressure is lower in more dorsal lung regions (the inverted closed triangle indicates more transpulmonary pressure in the ventral region and less transpulmonary pressure in the dorsal region). Such a vertical gradient of transpulmonary pressure causes a heterogeneous distribution of lung aeration. Esophageal pressure is a good surrogate for local pleural pressure in the regions adjacent to the esophageal balloon where atelectasis usually occurs. Therefore, setting PEEP using expiratory esophageal pressure to prevent dorsal atelectasis makes sense. To prevent alveolar collapse, PEEP should be titrated for transpulmonary pressure to be greater than or equal to 0. For example, if the absolute esophageal pressure is 5 cmH_2O, PEEP needs to be set at 5 cmH_2O to make the transpulmonary pressure greater than or equal to 0. ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; PL, transpulmonary pressure; P_{pl}, pleural pressure.

recruitability. The median R/I was 0.68, separating a high recruiter and a low recruiter. In high recruiters, high PEEP in conjunction with the prone position resulted in the highest oxygenation and lowest amount of lung collapse (measured as dependent silent space in electrical impedance tomography [EIT]) without increasing nondependent overinflation (measured as nondependent silent space in EIT). In low recruiters, low PEEP in conjunction with the prone position resulted in better oxygenation, less dependent silent spaces, and less nondependent silent spaces (Figure 3). Of note, the R/I ratio was not altered by changing position in all patients. Thus, the measurement of the R/I ratio at the bedside is quite useful for predicting the response to PEEP and to maximize the benefits of higher PEEP and minimize the adverse effects of high PEEP.

Electrical impedance tomography

EIT, which allows visualization of lung ventilation in real time, has become available at the bedside. EIT data were recorded continuously with 32 electrodes placed around the chest at the level of the fourth and fifth intercostal space. Reconstructed EIT images represent relative impedance changes for each pixel (delta Z) compared with a convenient reference taken at the beginning of data acquisition.[41]

EIT is able to estimate the amounts of collapsed tissue and overdistended tissue by performing decremental PEEP steps.[42] By sequentially measuring the EIT-derived regional Crs for each pixel, it is possible to quantify the amounts of tissue that (1) recollapse during the trial, excluding them from ventilation (pixel compliance decreases during decremental PEEP steps), and (2) are brought back to adequate ventilation, previously impaired by overdistension (pixel compliance increases during decremental PEEP steps).[41] The optimal PEEP is then considered as the PEEP where the amounts of collapsed tissue and overdistended tissue are compromised (ie, the crossover point between two curves of lung collapse and overdistension). In a randomized controlled trial conducted on scheduled surgical patients with body mass index >30 kg/m^2, the authors reported that such

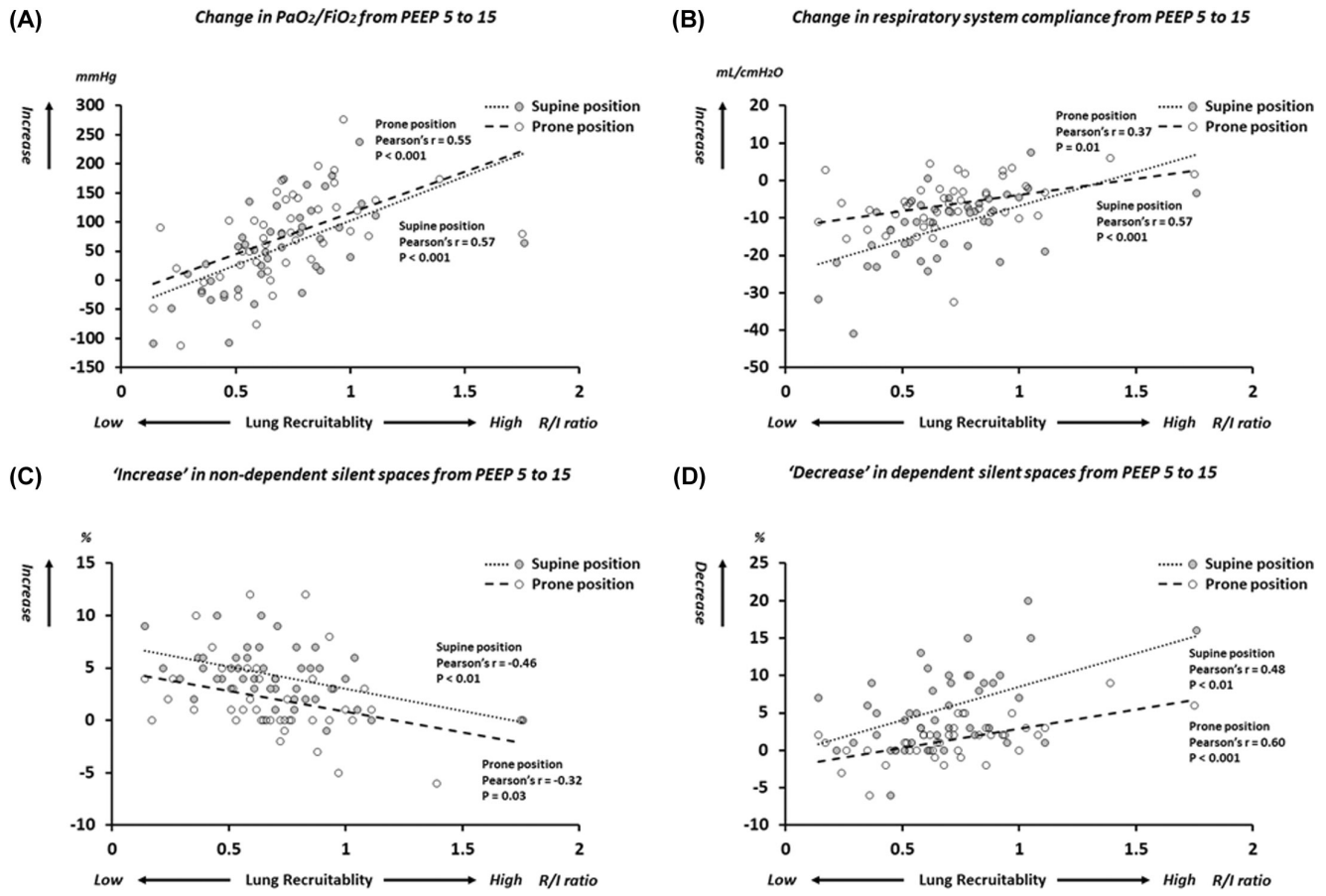

FIGURE 3 Prediction of response to PEEP using the R/I ratio. Correlation between R/I ratio and (A) "increase" in PaO_2/FiO_2, (B) "increase" in respiratory system compliance, (C) "increase" in nondependent silent spaces, (D) "decrease" in dependent silent spaces when applying high PEEP in each body position. The R/I ratio was measured when releasing PEEP from 15 to 5 cmH_2O in each position. Gray circles and white circles represent values obtained from the supine position and prone position, respectively. The black short-dot line and long-dot line represent the linear regression in the supine position and in the prone position. In both positions, the higher the R/I ratio was, the more PaO_2/FiO_2 improved (A), the more respiratory system compliance improved (B), the less nondependent silent spaces increased (C), and the more dependent silent spaces decreased (D) when applying high PEEP. FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PaO_2, arterial oxygen pressure; R/I ratio, recruitment-to-inflation ratio. Reproduced from Taenaka, H. et al. *Crit Care* **27**, 152 (2023).

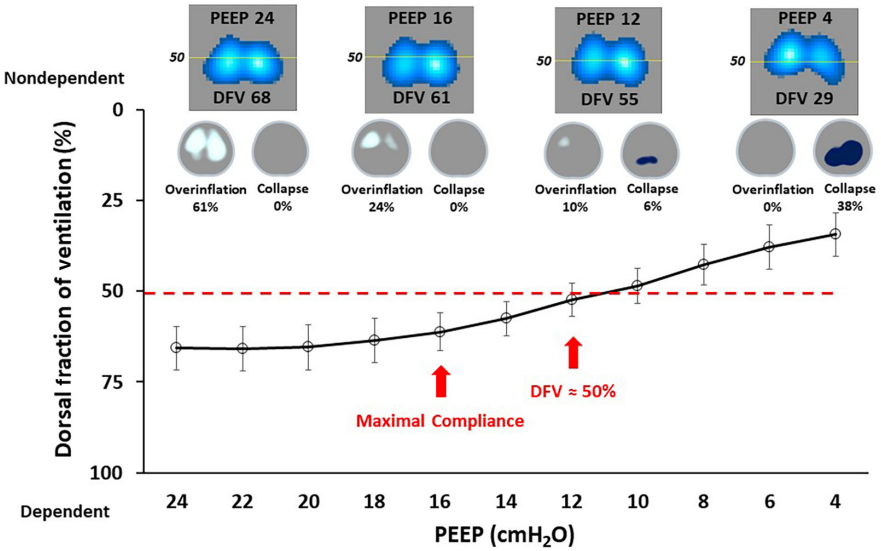

FIGURE 4 Distribution of lung aeration and respiratory compliance in experimental injury. Representative electrical impedance tomography images illustrating DFV and concomitant distribution of overinflation and collapse. Higher PEEP levels shifted DFV to dependent lungs because of nondependent overinflation. Decreasing PEEP to 12 cmH_2O achieved homogeneous ventilation, and this was associated with less hyperinflation. Further decreases in PEEP shifted DFV to nondependent lung as a result of dependent lung collapse. The dashed red line indicates DFV = 50%. Note: at PEEP 16 cmH_2O, Crs is maximum, but the DFV remains in dependent lungs because of (nondependent) overinflation. Crs, respiratory system compliance; DFV, dorsal fraction of ventilation; PEEP, positive end-expiratory pressure.
Modified from Yoshida, T., et al. *Am J Respir Crit Care Med* **200**(7): 933–937 (2019).

PEEP derived from EIT reduced the amount of atelectasis and thus drove pressure.[43]

Yoshida et al[44,45] coined the concept of "dorsal fraction of ventilation (DFV).". This reflects the distribution of tidal ventilation along the ventral–dorsal axis, and when the bulk of the ventilation is at the midpoint (DFV = 50%), this represents homogeneously distributed ventilation. DFV may be a useful indicator to avoid lung collapse and overdistension induced by insufficient or excessive PEEP (Figure 4). This is because PEEP can markedly change the distribution of ventilation as visualized by EIT. If PEEP is insufficient and collapse remains high in the dependent lung, then ventilation is predominantly nondependent (DFV < 50%). Overinflation in the nondependent lung can be detected by the shift of ventilation to the dependent lung (DFV > 50%). The DFV can be simply obtained from the EIT monitor, not requiring decremental PEEP steps or recruitment maneuvers.

To further reduce mortality in ARDS, we strongly believe that ventilatory strategies need to be evolved to "individualized" from "one-size fits all" strategies by detecting each subgroup/phenotype response to specific interventions (Figure 5).

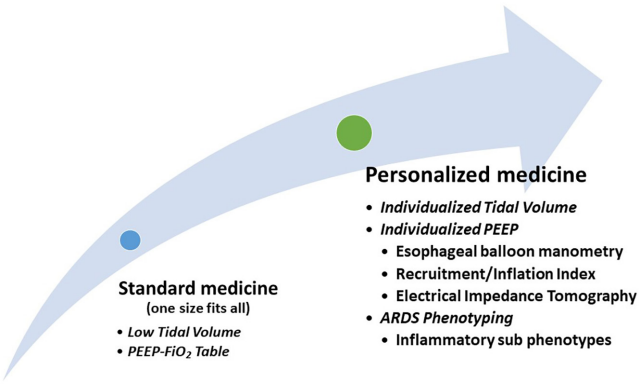

FIGURE 5 Personalized medicine implemented in lung-protective ventilation strategy. To protect the nondependent "baby" lung, the clinician targets and limits global parameters such as tidal volume and plateau pressure because the ARMA trial found benefits of a lung-protective ventilation strategy in ARDS. ARDS is a biologically and physiologically heterogeneous syndrome but not a disease with a single mechanism that is responsive to singular intervention. To further decrease mortality in ARDS, ventilatory strategies need to be tailored by detecting each subgroup's response to specific interventions. Currently, ventilatory strategies based on driving pressure or individualized PEEP are good candidates for personalized medicine in ARDS. ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.

CONCLUSION

Since the ARMA trial found the benefits of a lung-protective ventilation strategy in patients with ARDS, many efforts have been made to identify ventilatory strategies minimizing ventilator-induced lung injury, but thus far, the majority of clinical trials regarding supportive care and pharmacological interventions have failed to improve outcomes. This is probably because heterogeneous groups of patients from biological, physiological, or morphological points of view are included as a single clinical entity of ARDS. Thus, ventilatory strategies should be tailored by identifying subgroups likely to respond to specific interventions.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data are available.

ETHICS STATEMENT

Approval of the research protocol: Not applicable.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

ORCID

Takeshi Yoshida https://orcid.org/0000-0002-4695-5377

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