Acute Respiratory Distress Syndrome: Challenge for Diagnosis and Therapy

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Abstract

Objective: Acute respiratory distress syndrome (ARDS) is a devastating clinical syndrome whose diagnosis and therapy are still in question. The aim of this review was to discuss the current challenge for the diagnosis and treatment of ARDS.

Data Sources: Data sources were the published articles in English through December 2017 in PubMed using the following key words: “acute respiratory distress syndrome,” “definition,” “diagnosis,” “therapy,” “lung protective strategy,” “right ventricular dysfunction,” and “molecular mechanism.”

Study Selection: The selection of studies focused on both preclinical studies and clinical studies of therapy of ARDS.

Results: The incidence of ARDS is still high, and ARDS causes high intensive care units admissions and high mortality. The Berlin Definition proposed in 2012 is still controversial owing to lack of sensitivity and specificity. ARDS is still under recognition and it is associated with high mortality. Lung protective strategies with low tidal volume (VT) and lung recruitment should consider the physiology of ARDS because ARDS presents lung inhomogeneity; the same low VT might increase local stress and strain in some patients with low compliance, and lung recruitment could injure lungs in ARDS patients with low recruitability and hemodynamic instability. Acute cor pulmonale is common in severe ARDS. ARDS itself and some treatments could worsen acute cor pulmonale. Molecular understanding of the pathogenic contributors to ARDS has improved, but the molecular-associated treatments are still under development.

Conclusions: ARDS is a devastating clinical syndrome whose incidence and mortality has remained high over the past 50 years. Its definition and treatments are still confronted with challenges, and early recognition and intervention are crucial for improving the outcomes of ARDS. More clinical studies are needed to improve early diagnosis and appropriate therapy.

Key words: Acute Respiratory Distress Syndrome; Diagnosis; Mechanical Ventilation; Therapy

Introduction

Acute respiratory distress syndrome (ARDS) is a devastating clinical syndrome caused by various conditions such as infection and trauma.[1] During the last five decades, a better understanding of the epidemiology, pathophysiology, and pathogenesis of ARDS has led to new treatment strategies that improved survival rates significantly in patients with ARDS. However, the mortality of severe ARDS is still over 40.0%. Early recognition of ARDS and optimized management are crucial for outcome improvement.

Huge Burden of Acute Respiratory Distress Syndrome

ARDS is a common disease with a high variation of incidence worldwide. Epidemiological studies of ARDS have revealed an incidence of 10.1 per 100,000 person-years in South America, 17.9/100,000 person-years in Europe, 34/100,000 person-years in Australia, and 78.9/100,000 person-years in the USA.[3-6]

In intensive care units (ICUs), the incidence of ARDS is 7.1–12.5% in European countries. A global study conducted over fifty countries showed that 10.4% (95% confidence interval [CI], 10.0–10.7%) ICU patients developed ARDS. Similarly, variation was found in this study with an incidence...
Impact of Severe Acute Respiratory Failure (Lung SAFE) study, 60.2% of all patients with ARDS were clinician recognized, and the clinician’s diagnosis of ARDS ranged from 51.3% (95% CI, 47.5–55.0%) for mild ARDS to 78.5% (95% CI, 74.8–81.8%) for severe ARDS.

Several factors influence the early diagnosis of ARDS. Higher nurse-to-patient ratios, higher physician-to-patient ratios, younger patient age, lower PaO2/FiO2 ratio, and the presence of pneumonia or pancreatitis were factors independently associated with higher probability of clinician recognition.

There are still some factors associated with a lower probability of early recognition of ARDS. Absence of a risk factor and presence of concomitant cardiac failure were associated with reduced likelihood of clinician recognition of ARDS.

Tidal Volume Should Be Individualized

Although low tidal volume (VT) has been proved to decrease ARDS mortality, 6 ml/kg predicted body weight (PBW) VT is not suitable for all ARDS patients. Terragni et al. found that VT of 6 ml/kg PBW and plateau pressure of 30 cmH2O might not be sufficient to protect two-third of ARDS patients from dynamic hyperinflation. In fact, nonphysiological lung strain and stress could induce ventilator-induced lung injury (VILI), either globally or locally. It has been found that dynamic strain is still higher in many ARDS patients ventilated with even 6 ml/kg PBW. To minimize VILI, it is more reasonable to normalize VT to individual lung size. A former study showed that pulmonary compliance is associated with end-expiratory lung volume (EELV). To address this issue, airway driving pressure (quotient of VT/Crs) is proposed to substitute for lung dynamic strain. Amato et al. used multilevel mediation analysis to analyze individual data from 3562 patients with ARDS enrolled in nine randomized trials; they showed that decreases in driving pressure due to changes in ventilator settings were strongly associated with increased survival. Further study is needed to demonstrate whether driving pressure could be a goal of the individualized setting of VT in itself.

Airway driving pressure could be used as a safety limit during VT titration at the bedside. It has been demonstrated that driving pressure during mechanical ventilation is directly related to stress forces in the lung. Optimal cutoff values for airway driving pressure of 15.0 cmH2O and 16.6 cmH2O were considered as stress equal to or greater than 24 cmH2O and 26 cmH2O, respectively. In the clinical scenario, airway driving pressure is affected by chest wall compliance and spontaneous breathing. Inhibition of spontaneous breathing might be necessary during the measurement of airway driving pressure. However, routine measurement of transpulmonary driving pressure is not suggested since linear regression between transpulmonary and airway driving pressure has been found in 150 ARDS patients.

In severe ARDS patients, a lower VT strategy for lung protection might be followed by refractory hypoxemia or hypercapnia. In this scenario, extracorporeal membrane
The CIOR to the study of Guérin et al. The initial time of ECMO in patients with ARDS remains controversial, but the early use of ECMO could protect lungs from VILI. Indeed, ECMO is one of the most effective methods for lung protection, allowing very low VT leading to “lung rest.”

Pathophysiological Characteristics Guiding Lung Recruitment and Positive End-Expiratory Pressure Titration

Lung recruitment maneuvers (RMs) will be beneficial when properly applied to appropriately selected patients with high lung recruitability. A meta-analysis of six clinical trials has suggested RMs with higher PEEP-reduced mortality in patients with moderate and severe ARDS, but this finding has not been confirmed in randomized clinical trials. Recently, a large randomized clinical trial compared patients treated with the RMs and titrated PEEP with those managed with conventional PEEP in moderate-to-severe ARDS (PaO2/FiO2 ≤200). The result showed that a strategy with lung recruitment and titrated PEEP compared with the control group increased 28-day all-cause mortality, and RMs were associated with pulmonary complication in patients with moderate-to-severe ARDS. There are several reasons for the surprising results. First, RMs are suitable for high recruitability patients, but this study recruited more pneumonia patients, which had been demonstrated to have low lung recruitability; second, the pressure in the RM group is higher than that in former studies, which could increase the incidence of pneumothorax and barotrauma, complications of which are disastrous for severe ARDS; third, there are more septic shock patients in this study, and RMs could lead to hemodynamic variation, which might be the reason why the mortality is high in the RM group; fourth, the relatively high recruitment pressure will deteriorate hemodynamic stability and lead to more fluid administration; and fifth, RMs might be more beneficial in the early phase of ARDS, but the RMs were used for 7 days in this study. RMs remind clinician, not only severity of ARDS, but lung recruitability, phase of ARDS, recruitment pressure limitation, and hemodynamic stability should also be considered.

Prone position ventilation is another method of lung recruitment, especially for ARDS patients with low lung recruitability. Due to its beneficial effects in improving ventilation-perfusion matching, increasing EELV, and decreasing VILI by a more uniform distribution of VT through lung recruitment and alterations in chest wall mechanics, prone position ventilation should be considered in the early phase of ARDS patients with PaO2/FiO2 <150 mmHg (1 mmHg = 0.133 kPa). According to the study of Guérin et al. in patients with severe ARDS, early application of prolonged prone-positioning sessions for at least 16 h significantly decreased 28-day and 90-day mortality. With respect to the duration of the prone position, it has been strongly recommended that adult patients with severe ARDS receive prone positioning for more than 12 h/day.

Although the optimal approach to PEEP titration has not yet been established, oxygenation-based PEEP titration is the most commonly used method related to lung recruitability. The ARDSNet FiO2-PEEP table is one of the simple oxygenation-based methods for initial PEEP setting. Furthermore, the oxygenation response should be considered during PEEP titration. Goligher et al. found that patients with a positive oxygenation response (P > 25 mmHg increase in PaO2/FiO2) of higher PEEP had lower mortality than those without a positive oxygenation response (crude mortality rate: 31.0% vs. 54.0%, adjusted odds ratio [OR]: 0.36, 95% CI: 0.23–0.58). These results indicated that higher PEEP will benefit patients with a positive oxygenation response of PEEP. Since lung recruitability is associated with the severity of ARDS, setting PEEP according to ARDS severity might be a simple but physiologically sound method. Gattinoni et al. suggested that PEEP ranges of 5–10, 10–15, and >15 cmH2O should be used in mild, moderate, and severe ARDS, respectively. Individualized PEEP titrated by EIT, compliance, and transpulmonary pressure are helpful in selected ARDS patients.

Acute Cor Pulmonale Should Not Be Ignored

Acute cor pulmonale (ACP) is common in severe ARDS patients and is always ignored. The prevalence rate of echocardiographically evident ACP in ARDS ranges from 22.0% to 50.0%. Treatment of ACP in ARDS includes optimization of right ventricle preload and afterload; increased right ventricle contractility, pulmonary vasodilators, and lung protective ventilation are the important methods for reducing right ventricle afterload. For severe ACP, RMs, prone ventilation, and extracorporeal life support can reverse the physiological causes of ACP and facilitate “RV-protective” ventilation; however, ARDS mortality has not been verified in clinical studies.

Understanding of Molecular Mechanism for Acute Respiratory Distress Syndrome

Novel analytical techniques have been conducted for some of these accepted markers to refine ARDS endotypes or to serve as enrichment markers in future trials. Genome-wide association studies, next-generation sequencing, gene expression profiling, proteomics and metabolomics, and microbiome analysis have been used to select genetic variation and changes of expression of proteins and metabolites. Improved molecular understanding of the pathogenic contributors to ARDS could lead to individualized therapy for the inhomogeneous syndrome and could improve outcomes in the future.
ARDS has been a devastating clinical syndrome during the past 50 years, and its incidence and mortality remain high. The definition and treatment of ARDS are still confronted with challenges, and early recognition and intervention is crucial for improving the outcomes of ARDS. Precise lung protective strategy and early use of ECMO could improve the mortality rate of severe ARDS. More clinical studies are needed to improve early diagnosis and appropriate therapy.

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**Conflicts of interest**

There are no conflicts of interest.

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急性呼吸窘迫综合征：面临的挑战

摘要

目的：急性呼吸窘迫综合征(ARDS)是临床常见的危重症，往往导致患者预后不良。然而，ARDS的诊断与治疗仍面临很多的困难。本文综述了目前ARDS在诊疗过程中面临的挑战与困境。

data-source：以“急性呼吸窘迫综合征”、“定义”、“诊断”、“治疗”、“肺保护性通气”、“右心功能障碍”和“分子机制”为关键词在PubMed上搜索截止到2017年12月的相关英文文献。

研究选择：入选的文章必须涉及ARDS治疗进展的临床前与临床研究。

结果：目前ARDS的发病率、ICU住院率及病死率仍较高。尽管ARDS柏林诊断标准提出已经近5年，但这一诊断仍存在争议，对ARDS诊断的敏感性和特异性仍不高。临床对于ARDS的诊断仍不够及时和准确，而这往往导致ARDS不良预后。小潮气量及肺复张为基础的肺保护性通气需要基于患者的病理生理变化，由于ARDS的不均一性，同样的潮气量会导致局部应力及应变的增加，而且对于低可复张或血流动力学不稳定的患者，肺复张往往会加重肺损伤并导致循环进一步的恶化。对于重度ARDS，急性肺心病是常见的合并症，并且患者的病情及临床的一些不适当的干预治疗往往会导致患者急性肺心病的加重。分子生物学的进步有助于深入理解ARDS病理生理变化，但是分子层面的治疗仍需要进一步的研究证实。

结论：虽然ARDS的发现距今已经有50年，但目前的发病率及病死率仍较高，而且目前的诊断和治疗仍面临巨大的挑战，早期诊断和干预能够改善ARDS的临床预后，但需要更多的临床证据优化诊疗措施。