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FOCUS EDITORIAL

# Focus on ARDS

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Since 1967, when first described, ARDS has been widely recognized as a major health problem worldwide, carrying a high morbidity and mortality [1–3]. This focus editorial summarizes recent advances about the incidence, pathophysiology, right ventricular dysfunction, and mortality of ARDS.

Despite the attempt to homogenize its definition following the publication of the Berlin criteria, there is still a high heterogeneity in the epidemiology of ARDS across the world [3]. Indeed, estimates of the incidence of ARDS are highly variable, ranging from less than 2 to more than 70 cases per 100,000 person-years, with the most recent study on the topic suggesting a higher incidence in Europe, North America, and Oceania compared to South America, Asia, and Africa [2, 3]. However, it is important to emphasize that this scenario could only reflect the under-recognition of this syndrome [3]. Recent reports suggest a progressive decline of the incidence of ARDS. In a study conducted in Rochester, cases fell by half between 2001 and 2008 while mortality remained stable [4]. Nearly all of the reduction in the incidence was observed in hospital-acquired ARDS, suggesting that ARDS could be prevented through strategies addressing its related risk factors [4, 5]. However, in some instances, patients meeting the Berlin criteria for ARDS lack exposure to common risk factors [6]. It was recently reported that the prevalence of patients with ARDS but without common risk factors was as high as 7.5% [6]. According to medical history, bronchoalveolar lavage fluid cytology, and chest computed tomography (CT) scan patterns, four etiological categories were identified in this group of patients: immune, drug-induced, malignant, and idiopathic [6]. The overall ICU mortality rate was higher in patients lacking common risk factors as compared to their counterparts, even after adjustment for potential confounding factors [6].

It is already well known that ventilator-induced lung injury contributes to ARDS-associated mortality [2, 3]. Recently, some biological markers have been proposed as potential biomarkers of ARDS, such as the soluble form of the receptor for advanced glycation end-products (sRAGE). This biomarker is a transmembrane receptor that can bind multiple ligands resulting in intracellular signaling, leading to activation of the proinflammatory transcription factor nuclear factor κB [7]. Plasma levels of sRAGE could change according to ventilator settings in ARDS patients, as recently suggested by a study describing a significant decrease of sRAGE 1 h after a recruitment maneuver followed by an increase toward baseline values 4 h after the maneuver [7]. It has also been shown that sRAGE is higher in non-survivors than survivors in early pediatric ARDS and strongly correlated with number of non-pulmonary organ failures [8]. Other biomarkers of endothelial injury are also investigated in ARDS patients. Higher levels of circulating endothelial cells were found in the blood of patients with moderate-to-severe ARDS as compared to those with mild or without ARDS [9]. Soluble thrombomodulin (sTM) is another biomarker of endothelial injury investigated in ARDS patients [10]. A recent post hoc analysis of a huge cohort showed that higher plasma levels of sTM are associated with increased mortality in ARDS patients [10]. Also, the lack of association between the sTM levels and genetic variants reported in this latter study suggests that the increased levels of sTM may reflect severity of endothelial damage rather than genetic heterogeneity [10]. Finally, the prognostic value of plasma soluble urokinase plasminogen activator receptor (suPAR) was recently assessed in a series of 632 ARDS patients, and increased levels of plasma suPAR were significantly associated with ICU mortality [11]. Altogether, these promising endothelial biomarkers may guide the development of future strategies targeting endothelial stabilization,

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repair, and/or functional replacement in certain ARDS categories. However, their prominent involvement during indirect lung injury likely reflects increased inflammation and both pulmonary and systemic endothelial damage. Indeed, the severity of pulmonary vascular injury is quite disparate between ARDS patients and may prevail during indirect injury.

Right ventricular dysfunction may reflect the presence of lung vascular dysfunction during ARDS. In a series of more than 750 patients, the prevalence of acute cor pulmonale during ARDS was found to be 22%, with severe forms being associated with increased mortality [12]. A simple clinical risk score of acute cor pulmonale was proposed, including four variables: pneumonia as a cause of ARDS, driving pressure at least 18 $cmH_2O$, $PaO_2/FiO_2$ ratio less than 150 mmHg, and arterial $PaCO_2$ at least 48 mmHg [12]. This score may help in selecting patients to be monitored for early identification of acute cor pulmonale, preferably with transesophageal echocardiography [12]. Indeed, recent studies and reviews have reinforced the seminal role of ultrasound in general, and transesophageal echocardiography in particular, in the diagnostic workup and monitoring of ARDS patients [13]. The direct assessment of pulmonary vascular dysfunction at the bedside is still a clinical challenge, but emerging techniques like electric impedance tomography may provide informative data on regional distribution of lung perfusion in the near future [14].

The majority of the patients diagnosed with ARDS present it in its moderate form, with an in-hospital mortality rate around 40% [3]. There is a high variability in reported mortality of ARDS patients, probably reflecting differences in care, risk factors, ability to diagnose, and resource availability. However, in general, recent studies suggest a decrease in mortality rate from ARDS probably due to better ventilatory care and control of modifiable risk factors associated with mortality [15].

While we are interested in developing new concepts or techniques to improve mechanical ventilation care or associated measures, we should have in mind that this type of support cannot cure the patient if the cause of ARDS is not promptly identified and the resulting treatment quickly initiated. This is particularly the case in ARDS related to a direct lung injury which needs a systematic approach based on bronchoalveolar lavage and blood samples to identify the cause of ARDS and to guide the correct treatment [13].

For more information regarding ARDS, there is a recent series of up-to-date review articles published in *Intensive Care Medicine* for the 50th birthday of the first description of ARDS.

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**Compliance with ethical standards**

**Conflicts of interest**
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