The new Berlin definition:
What is, finally, the ARDS?

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Acute respiratory distress syndrome (ARDS) was first described in 1967, by Ashbaugh and Petty[1], who described 12 patients, admitted to the Intensive Care Unit (ICU) with severe acute respiratory failure from multiple causes needing mechanical ventilatory support. The clinical condition of all the patients was characterized by an unusually long-lasting tachypnoea in association with persistent hypoxaemia and bilateral lung opacities on chest X-ray. Their lung compliance was significantly reduced, leading to difficulties in artificial ventilation. The mortality of the syndrome was high: 7 of the 12 subjects died (60%). After this first description, ARDS became recognized as a progressively common clinical entity that physicians are called upon to deal with.

In the following years, concerted efforts were made to establish an accurate definition of ARDS[2], for both research and clinical purposes. It was recognized that such an endeavour could form the basis for standardization of the various different experimental and clinical studies, in order to determine accurately the incidence and pathophysiology of the syndrome, with a view to facilitating its early diagnosis, effective treatment and accurate prognosis.

In 1988, John Murray proposed a definition based on the so-called lung injury score (LIS)[3]. This definition included 4 criteria: opacities on chest X-ray, hypoxaemia, applied PEEP and elasticity of the respiratory system. Each parameter could be assigned 1-4 points, depending on the severity of respiratory injury. A total score of 0 reflected normal lung function, 1-2.5 indicated slight-to-moderate lung injury, while LIS higher than 2.5 was suggestive of severe lung injury or ARDS. Despite extensive use of LIS in clinical research, its adoption in everyday clinical practice was limited because of two significant pitfalls: lack of specificity (absence of reported risk factors and inclusion of cases with cardiogenic pulmonary oedema as a possible cause of lung injury) and uncontrolled prognostic validity.

The lack of a commonly accepted definition of ARDS across the scientific community continued for a long time to obstruct the design of accurate epidemiological studies. In the early 1990s, for instance, the reported incidence and mortality of ARDS exhibited significant variance among different studies, ranging from 10% to 90%[4]! Such discrepancies led the American Thoracic Society (ATS) and the European Society of Intensive Care Medicine (ESICM), with the concomitant support of National Heart, Lung and Blood Institute

(NHLBI), to organize a task force of leading experts, with the objective of proposing a commonly accepted unified definition. Thus, in 1994, the expert panel published for the first time the American and European Consensus Conference (AECC) criteria for the diagnosis of ARDS[5]. According to this definition, ARDS must be characterized by: 1. Acute onset, 2. Severe hypoxaemia (PaO_2/FiO_2<200), 3. Bilateral opacities on chest X-ray, and 4. Absence of left ventricular failure, confirmed by clinical examination or right heart catheterization (PCWP <18 mmHg). The AECC definition introduced into the literature a new term: acute lung injury (ALI), which was broader than ARDS, as it included disorders with a less severe degree of hypoxaemia (PaO_2/FiO_2<300), but with the same causes and pathophysiology. The major advantage of the new definition, which made it more easily applicable in current clinical practice than the earlier versions, was that it is based mainly on clinical criteria rather than physiological parameters. This effort boosted both epidemiological and interventional clinical studies over the ensuing years; for example, the landmark NIH ARDS Network study that showed significant reduction in mortality after administration of low tidal volumes to patients with ARDS, was based on the new AECC definition.

The limitations of the new definition, however, became progressively apparent during its broader implementation in both everyday clinical practice and clinical research[6]. Such limitations, for instance, are: the term 'acute onset' is not defined (i.e., within hours, days or weeks?; the degree of hypoxaemia may vary significantly depending on PEEP levels (7); the agreement in interpretation of radiological findings remains modest even between experts[8]; threshold values of PCWP <18 mmHg (in the case of measurement) are not always discriminative, since many patients with ARDS exhibit values >18 mmHg, due to increased intra-thoracic pressure or fluid overload after resuscitation[9]; finally, the term ALI is commonly misused, referring to both patients with 200<FiO_2<300 mmHg and those suffering from ARDS with FiO_2<200.

In conclusion, 18 years after the first unified definition, circumstances have changed in such a way as to make desirable a revision of the AECC criteria, although the widespread use of the AECC criteria by the majority of ARDS studies published to date could possibly limit enthusiasm for extensive revision. Compatibility with the old, accepted definition therefore appeared to be a basic prerequisite for revision of the criteria, facilitating comparison between old and future epidemiological and interventional studies.

THE NEW DEFINITION

ESICM, in collaboration with ATS and Society of Critical Care Medicine (SCCM) took the initiative once more, and gathered together a panel of experts in Berlin, who first proposed a revised set of criteria for the diagnosis of ARDS and then checked their validity. Subsequently, in June 2012, the resultant new ARDS definition was published in a high impact factor journal (Table 1)[10]. A brief critical reappraisal follows of the methodology of the concept and the individual revised criteria of the new definition.

ΠΙΝΑΚΑΣ 1. Ο ορισμός του Βερολίνου για το ARDS (10)

Acute respiratory distress syndrome (ARDS)			
Timing	Within 1 week of a known clinical insult or new or worsering respiratory symptoms		
Chest imaging[a]	Bilateral opacities – not fully explained by effusions, lobar/lung collage, or noduls		
Origin of edema	Respiratory failure not fully explained by cardiac failure of fluid overload Need objective assessment (eg., echocardiography) to exclude hybrostatic edema if no risk factor present		
	Mild	Moderate	Severe
Oxygenation[b]	200<PaO_2/FiO_2 ≤ 300 with PEEP or CPAP ≥5 cmH_2O[c]	100<PaO_2/FiO_2 ≤ 200 with PEEP or CPAP ≥5 cmH_2O	PaO_2/FiO_2 <100 with PEEP or CPAP ≥5 cmH_2O

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, position and expiratory pressure

[a]Chest radiograph or computed tomography scan. [b]If attitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2 × (barometric pressure/760)].

[c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Methodology

Initially, the expert panel proposed a draft definition differentiating ARDS into 3 subcategories, based on the degree of hypoxaemia: benign (200 mm Hg <PaO_2/FIO_2 ≤300 mmHg), moderate (100mmHg <PaO_2/FIO_2 ≤200mmHg) and severe (PaO_2/FIO_2 ≤100 mmHg) ARDS. In addition, for the last category, 4 ancillary physiological variables were set: 1. Radiological opacities on chest X-ray involving 3 or 4 quadrants, 2. Compliance of the respiratory system ≤40 ml/cm H_2O, 3. PEEP ≥10cm H_2O, and 4. Corrected minute expiratory ventilation ≥10L/min. This draft definition was then evaluated empirically using large data sets of ARDS patients. Specifically, the findings from a meta-analysis including 4,188 patients with ARDS from 4 multicentre studies and 269 patients from 3 single-centre studies were used, that included various different physiological variables. Since it was demonstrated that adding the 4 ancillary variables to the criteria of the new definition did not improve its prognostic value significantly, they were omitted from the final definition[10]. Finally, in comparison with the original AECC criteria, the new definition was found to exhibit better prognostic value in terms of mortality.

In conclusion: for the first time, a definition of ARDS is characterized not only by its feasibility and reliability, but also by its validity.

Terminology

As mentioned above, in the new definition, the term ALI has been abandoned, while 3 subcategories of ARDS have been proposed, based on the severity of hypoxaemia. The new terminology is expected to put an end to the confusion derived from the AECC criteria, where, for example, the medical literature contains such descriptions of the syndrome as 'ALI/ARDS'! In addition, the term 'severe ARDS' might identify a subgroup of patients who could benefit from specific therapeutic interventions, such as prone positioning, high frequency ventilation (HFV) or extracorporeal mechanical oxygenation (ECMO).

Time of onset

One week is now clearly defined as the time window necessary for the manifestation of ARDS associated with a known risk factor. The adoption of this criterion by the expert panel was based on findings from recent epidemiological studies, which have shown that the majority of ARDS patients develop the syndrome within 72 hours of exposure to a known risk factor, and the whole group of patients within 7 days[11].

Imaging of the chest

Radiological findings have been defined more clearly. The particular reference to bilateral opacities that cannot be fully explained by effusions, lobar/lung collapse, or nodules, along with findings on computed tomography CT) scan of the chest (not, however, obligatory) is expected to improve the reliability of the imaging criteria. In this context, the expert panel suggested and displayed a representative sample of chest X-rays[10].

Risk factors/Causes of pulmonary oedema

The risk factors for development of ARDS are known (Table 2), but the expert panel highlighted the importance of the exclusion of cardiogenic pulmonary oedema. Whenever respiratory failure cannot be fully attributed to heart failure or fluid overload, then the patient is probably suffering from ARDS. Conversely, however, in the event that known risk factors are absent, then cardiogenic pulmonary oedema must be absolutely excluded. In the new definition, PCWP threshold values have been omitted as a discrimination tool between the two types of pulmonary oedema, while echocardiography has been proposed as the gold standard for excluding left heart failure.

Oxygenation

Since PEEP application alters the reliability and specificity of the oxygenation index PaO2/FiO2 as a severity index of ARDS, the new definition suggests the application of a minimum level of PEEP 5 cm H_2O. In the benign form of the

TABLE 2. Risk factors for acute respiratory distress syndrome (ARDS) (10)

Pneumonia
Non-pulmonary sepsis
Aspiration of gastric contents
Major trauma
Pulmonary contusion
Pancreatitis
Inhalational injury
Severe burns
Non-cardiogenic shock
Drug overdose
Multiple transfusions or, transfusion-associated acute lung injury (TRALI)
Pulmonary vasculitis
Drowning

syndrome, this PEEP level can be applied through CPAP/NIV. In severe ARDS, using higher values of PEEP (>10 cm H_2O) with FiO_2 >0.7 did not increase the prognostic value of the new definition, in terms of mortality.

Further measurements

The expert panel suggested that certain additional diagnostic criteria, such as the amount of extra-vascular lung water, various different bio-markers, electrical impedance tomography and lung biopsy are either not feasible for application at the bedside or are lacking in adequate prognostic value[12].

The advantages of the new definition

Its formulation has a novel methodology. The combination of consensus between experts (expert opinion) and empirical reappraisal was adopted here for the first time. This could serve as an example for future more accurate definition of other syndromes in critical care medicine.

It is expected to boost clinical research, particularly in relation to severe ARDS, offering the possibility of more accurate assessment of the effectiveness of different forms of treatment.

Although not expected to change significantly the way things work in daily clinical practice, it could help those engaged in the diagnosis and treatment of ARDS understand each other more easily by adopting a more homogeneous concept of the syndrome.

Its publication in a high impact factor journal is expected to increase scientific interest in patients with ARDS. This could encourage the implementation of the clinical protocols that have been found to ameliorate prognosis, such as low tidal volume protective ventilation and restrictive protocols of fluid administration in haemodynamically stable patients.

A FINAL WORD

ARDS is a syndrome, meaning that it constitutes a common clinical phenotype of severe lung injury associated with many different direct or indirect causes[2]. The common clinical appearance and specific histopathological lesions (diffuse alveolar damage-DAD) allow it to be considered, for both clinical (standardization of supportive treatment) and research reasons, as a unified entity, despite its different causes. In other words, the word "syndrome" here imposes a universal definition with an inherent disadvantage, i.e., lack of common aetiology. As a consequence, studies that aim at the development of new forms of treatment for different groups of patients recruited according to specific causes of ARDS have so far been limited. Such a handicap may confuse the interpretation of scientific results, as one particular form of treatment may be beneficial or not, depending on the differing aetiology.

Thus, if we wish to identify a weakness in the new Berlin ARDS definition, we would suggest the absence of inclusion of the specific aetiology. Better understanding of the pathogenesis of ARDS in the future is expected to unravel more clearly its identity (or multiple identities?) and provide us with even better definitions!

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