Comparison of the Berlin Definition for Acute Respiratory Distress Syndrome with Autopsy

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Rationale: A revised definition of clinical criteria for acute respiratory distress syndrome (ARDS), the Berlin definition, was recently established to classify patients according to their severity.

Objective: To evaluate the accuracy of these clinical criteria using diffuse alveolar damage (DAD) at autopsy as the reference standard.

Methods: All patients who died and had a clinical autopsy in our intensive care unit over a 20-year period (1991–2010) were included. Patients with clinical criteria for ARDS were identified from the medical charts and were classified as mild, moderate, or severe according to the Berlin definition using PaO2/FIO2 oxygenation criteria. Microscopic analysis from each pulmonary lobe was performed by two pathologists.

Measurements and Main Results: Among 712 autopsies analyzed, 356 patients had clinical criteria for ARDS at time of death, classified as mild (n = 49, 14%), moderate (n = 141, 40%), and severe (n = 166, 46%). Sensitivity was 89% and specificity 63% to identify ARDS using the Berlin definition. DAD was found in 159 of 356 (45%) patients with clinical criteria for ARDS (in 12, 40, and 58% of patients with mild, moderate, and severe ARDS, respectively). DAD was more frequent in patients who met clinical criteria for ARDS during more than 72 hours and was found in 69% of those with severe ARDS for 72 hours or longer.

Conclusions: Histopathological findings were correlated to severity and duration of ARDS. Using clinical criteria the revised Berlin definition for ARDS allowed the identification of severe ARDS of more than 72 hours as a homogeneous group of patients characterized by a high proportion of DAD.

Keywords: acute respiratory distress syndrome; acute lung injury; diffuse alveolar damage; mechanical ventilation

Acute respiratory distress syndrome (ARDS) was described for the first time in 1967 by Ashbaugh and colleagues (1). However, it was not until 1994 that an international American–European Consensus Conference (AECC) laid the foundations for the definition of ARDS, including the following clinical criteria (2): the recent onset of symptoms after a known risk factor, severe hypoxemia defined by a PaO2/FiO2 ratio less than 200 mm Hg, bilateral infiltrates on chest radiograph, and absence of cardiogenic pulmonary edema. However, this definition has been criticized because of its many limitations (3, 4). Indeed, the acute nature of symptoms was not specified, level of positive end-expiratory pressure (PEEP) was not taken into account in oxygenation criteria, and cardiogenic pulmonary edema was defined as an increase in pulmonary artery wedge pressure, whereas recent studies found that high pressures could coexist with ARDS (5, 6).

Identification of patients with more severe disease could be crucial to evaluate treatment in more homogeneous populations, and some authors have already suggested reviewing the clinical criteria for ARDS (3). For this reason, a revised definition of clinical criteria for ARDS, the Berlin definition, was recently established to classify patients according to their disease severity (7). ARDS was classified depending on oxygenation as mild, moderate, or severe if PaO2/FiO2 was, respectively, between 201 and 300 mm Hg, 101 and 200 mm Hg, or 100 mm Hg or less, using a minimal PEEP level of 5 cm H2O. Oxygenation criteria were well correlated to severity, with a respective mortality of 27, 32, and 45% in mild, moderate, and severe ARDS (7).

Diffuse alveolar damage (DAD), including hyaline membranes, edema, cell necrosis, or fibrosis, is the morphological hallmark of ARDS, as was described by Katzenstein and colleagues in 1976 (8). However, other diseases clinically resembling ARDS are not associated with the typical histological feature of DAD.

The main objective of our study was to evaluate the accuracy of the Berlin definition in mild, moderate, and severe ARDS by comparing the presence or absence of DAD at autopsy examinations of patients with clinical criteria of ARDS.

Some of the results of this study have been previously reported in the form of an abstract at the 2012 meeting of the European Society of Intensive Care Medicine in Lisbon, Portugal (9).

METHODS

Inclusion of Patients

Our usual practice is to systematically request consent for autopsy to relatives of patients who die in our intensive care unit (ICU). Thus,
we included all patients who died and had a clinical autopsy performed between 1991 and 2010 in the 18-bed ICU at the Hospital Universitario de Getafe after relatives gave informed consent. We excluded patients who were organ donors and those whose autopsies were legally mandated. We have previously compared the AECC definition with our autopsy findings from 1991 to 2002 (10). These patients were included in the present study, but were all reanalyzed from scratch using the Berlin definition for ARDS.

Clinical Criteria for ARDS: The Revised Berlin Definition

Medical charts were retrospectively reviewed by two intensivists blind to the autopsy findings to determine if patients had clinical criteria for ARDS at time of death. They recorded demographic variables (age, sex, severity score at ICU admission), reasons for ICU admission and mechanical ventilation, duration of mechanical ventilation, and date of the onset of risk factor for ARDS. Patients were considered to have a pulmonary risk factor for ARDS if they had the diagnosis of pneumonia, aspiration, inhalation or lung contusion, and an extrapulmonary risk factor for ARDS if they had the diagnosis of sepsis, shock, multiple trauma or transfusion, or pancreatitis. In patients with risk factors for ARDS, we collected ventilatory settings (tidal volume, respiratory rate, peak inspiratory pressure, PEEP, and $F_iO_2$), arterial blood gases results, and chest radiographs findings within the 48 hours before death. As plateau pressure was not measured on the whole period of the study we calculated dynamic compliance as tidal volume divided by peak inspiratory pressure minus PEEP.

According to the Berlin definition, patients were considered as having ARDS if they had: (1) acute respiratory failure not fully explained by cardiac failure or fluid overload, as judged by the treating physician; (2) bilateral opacities consistent with pulmonary edema on the chest radiograph or the computed tomography scan; and (3) onset within 1 week after a known clinical insult or new/worsening respiratory symptoms. Severity was defined according to oxygenation, and ARDS was considered as mild if $P_{A}O_2/F_iO_2$ was between 201 and 300 mm Hg, moderate if $P_{A}O_2/F_iO_2$ was between 101 and 200 mm Hg, and severe if $P_{A}O_2/F_iO_2$ was less than or equal to 100 mm Hg, in all cases using a PEEP level at least of 5 cm H$_2$O. Diagnosis of ARDS was established by consensus of the two intensivists and resolved by a third intensivist in case of discrepancies.

As ventilatory modalities have markedly changed over this 20-year period, especially with the use of protective ventilation strategy by reducing tidal volume (11), we decided to compare ventilatory settings and proportion of ARDS or DAD among patients at risk during the two decades from 1991 to 2000 and from 2001 to 2010.

In patients who met clinical criteria for ARDS at time of death, we also collected the duration of the time during which the patient maintained clinical criteria for ARDS (i.e., the time between the onset of ARDS and death, and the pattern of death). We considered refractory shock as the clinical syndrome associated with death if systolic blood pressure was persistently below 90 mm Hg during the 6 hours before death, refractory hypoxemia if oxygen saturation was persistently below 85% during the 6 hours before death, and refractory shock and hypoxemia if the two causes coexisted. Withdrawal of life support was also registered.

Pathologic Criteria for DAD

Postmortem study was performed within 12 hours of death. After removal of the thorax, the lungs were inflated with 10% formalin to a pressure of 35 cm H$_2$O and fixed in block with 10% formalin. After 48 hours, the lungs were cut into slices of 3-cm thickness. We took samples for microscopic analysis from each pulmonary lobe and additional samples from areas with macroscopic injuries. Two pathologists independently analyzed each sample, and a third pathologist resolved any discrepancies.

Criteria for the diagnosis of DAD included the presence of hyaline membranes plus at least one of the following: intra-alveolar edema, alveolar type I cell necrosis, alveolar type II cell (cuboidal cells) proliferation progressively covering the denuded alveolar-capillary membrane, interstitial proliferation of fibroblasts and myofibroblasts, or organizing interstitial fibrosis (8, 12). The presence of hyaline membranes was qualitatively assessed (yes or no), and patients were classified as DAD if they had hyaline membranes even if hyaline membranes were present in only one lobe, as this finding could represent an incipient form of DAD. Histological criteria for the diagnosis of acute pneumonia included the presence of intense neutrophilic infiltration in the interstitium and in the intra-alveolar spaces, and particularly around terminal bronchioles.

Statistical Analysis

All data are expressed as means (±SD) or proportions with 95% confidence interval (CI). Considering that patients who truly had ARDS were those who had DAD on autopsy examination, we calculated operative indices of clinical criteria using the Berlin definition for ARDS, including sensitivity, specificity, and likelihood ratios according to standard criteria (13). We evaluated the validity of the Berlin definition for ARDS, including all patients, and then including only patients with any risk factor for ARDS. We also evaluated the impact of severity (mild, moderate, and severe) and duration of ARDS on occurrence of DAD. The proportions and qualitative data were compared using the Chi-square test and quantitative data using the unpaired Student’s t test for normally distributed variables or the Kruskal-Wallis test. P values less than 0.05 were considered significant.

RESULTS

We analyzed 712 autopsies over a 20-year period (1991–2010), of which 448 patients had risk factors for ARDS (Figure 1). Among the 356 patients who met clinical criteria for ARDS using the Berlin definition, 49 (14%) were classified as having mild ARDS, 141 (40%) as having moderate ARDS, and 166

![Figure 1. Flow chart of patients who have had an autopsy over this time period. ARDS = acute respiratory distress syndrome.](image-url)
(46%) as having severe ARDS. Characteristics of patients with ARDS are given in Table 1. As compared with patients excluded because of cardiogenic pulmonary edema, patients with ARDS had more severe lung injury, their lungs were heavier, and they had DAD more frequently at autopsy.

**Sensitivity and Specificity of Clinical Criteria for ARDS**

Among the 448 patients with risk factors for ARDS, 163 patients (36%) met the pathologic criteria for DAD at autopsy, and only 4 patients presented DAD without clinical criteria for ARDS. The agreement between the clinical and the histopathologic diagnosis of ARDS and the operative indices calculated are given in Table 2.

Using DAD as the reference standard, the sensitivity and the specificity of the Berlin definition for the diagnosis of ARDS were, respectively, 89% (95% CI, 84–93%) and 63% (95% CI, 59–67%) in the entire group of autopsied patients.

In patients with any risk factor for ARDS, the sensitivity improved to 98% (95% CI, 94–99%), but the specificity fell to 31% (95% CI, 26–36%). The specificity of the definition increased to 46% (95% CI, 40–52%) for moderate and severe ARDS.

Using DAD or pneumonia as the reference standard, the sensitivity and the specificity of the Berlin definition were 88% (95% CI, 83–91%) and 37% (95% CI, 30–45%), respectively, in patients with any risk factor for ARDS. The specificity increased to 58% (95% CI, 51–65%) for moderate and severe ARDS.

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**TABLE 2. SENSITIVITY AND SPECIFICITY OF THE CLINICAL CRITERIA FOR THE DIAGNOSIS OF ACUTE RESPIRATORY DISTRESS SYNDROME ACCORDING TO THE BERLIN DEFINITION USING DIFFUSE ALVEOLAR DAMAGE OR PNEUMONIA AS THE REFERENCE STANDARD**

<table>
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<th>Clinical Criteria for ARDS</th>
<th>No Clinical Criteria for ARDS</th>
<th>% Sensitivity (95% CI)</th>
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<td>Using DAD as the reference standard</td>
<td>Mild, moderate, or severe ARDS</td>
<td>All patients with autopsy (n = 712)</td>
<td>159 197</td>
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<td>Moderate or severe ARDS</td>
<td>All patients with autopsy (n = 448)</td>
<td>159 197</td>
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<td>98 (94–99)</td>
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<td>Using DAD or pneumonia as the reference standard</td>
<td>Mild, moderate, or severe ARDS</td>
<td>All patients with autopsy (n = 712)</td>
<td>262 94</td>
<td>49 307</td>
<td>84 (80–88)</td>
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<td></td>
<td>Moderate or severe ARDS</td>
<td>All patients with autopsy (n = 448)</td>
<td>262 94</td>
<td>37 55</td>
<td>88 (83–91)</td>
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**Definition of abbreviations:** ARDS = acute respiratory distress syndrome; CI = confidence interval; DAD = diffuse alveolar damage; SAPS II = Simplified Acute Physiology Score II.
Among all patients who met clinical criteria for ARDS, DAD was found in 45% (159 of 356 patients). Histological findings of pneumonia coexisted in 98 patients with DAD (62%). Among the 197 patients with clinical criteria for ARDS without DAD, histopathologic findings were pneumonia ($n = 97, 49\%$), pulmonary abscess ($n = 6, 3\%$), tuberculosis ($n = 3, 1.5\%$), cancer infiltration ($n = 11, 5.5\%$), pulmonary embolism ($n = 9, 4.5\%$), acute pulmonary edema ($n = 9, 4.5\%$), pulmonary hemorrhage ($n = 12, 6\%$), interstitial pneumonia/fibrosis ($n = 9, 4.5\%$), and severe emphysema ($n = 14, 7\%$), whereas no pulmonary lesion was found in 27 patients (14%).

**Impact of Severity, Risk Factor, and Duration of ARDS on Occurrence of DAD**

Alterations of elastic properties of the respiratory system and the weight of the lungs depended on the severity of ARDS (see Table E1 in the online supplement). Patients with severe ARDS had a lower compliance of the respiratory system and their lungs were heavier at autopsy than patients with moderate and mild ARDS ($P < 0.001$ for both).

The presence of DAD was significantly correlated to severity of clinical criteria for ARDS and was 12% (6/49), 40% (56/142), and 58% (97/166) in patients with mild, moderate, and severe ARSD, respectively ($P < 0.01$ between all groups; Figure 2). The presence of DAD or pneumonia was found in 57% (28/49), 47% (94/141), and 88% (140/166) of patients with mild, moderate, and severe ARSD, respectively ($P < 0.01$ between the three groups).

The origin of ARDS had no influence on the occurrence rate of DAD, which was present in 49% (71/145) of patients with pulmonary ARDS and in 42% (88/211) of patients with extrapulmonary ARDS ($P = 0.18$).

Patients who met clinical criteria for ARDS for a longer time had a higher probability of DAD on autopsy examination (Figure 3). DAD was found in only 27% of patients who met clinical criteria for ARDS during less than 72 hours versus 62% of patients who met ARDS criteria during more than 72 hours ($P < 0.01$). The incidence of DAD was 69% (79/114) in patients who met clinical criteria for ARDS during more than 72 hours and who were classified as having severe ARDS (Figure 4).

**Temporal Changes on Occurrence of DAD**

During the second decade (2001–2010), patients with any risk factor for ARDS were ventilated with a lower tidal volume and a higher respiratory rate than during the first decade (1991–2000; Table E2). At time of death, patients during the first decade had lung injury of higher severity than patients during the second decade, as indicated by a lower PaO2/FIO2 ratio, a higher peak airway pressure, and a lower respiratory system dynamic compliance. Among patients with any risk factor for ARDS, the proportion of patients with clinical criteria for ARDS or DAD at autopsy was greater during the first decade than during the second decade (Figure 5).

**Pattern of Death in Patients with ARDS**

The patterns of death among the 356 patients with ARDS was refractory shock in 162 (45%), refractory hypoxemia in 39 (11%), refractory hypoxemia and shock in 52 (9%), withdrawal of life support in 75 (21%), sudden cardiac arrest in 45 (13%), and brain death in 3 (1%). Refractory hypoxemia was the clinical syndrome associated with death in 47% of patients with severe ARDS with full life support, excluding withdrawal of life support and brain death (26% with refractory hypoxemia and 21% with refractory hypoxemia and shock; Figure 6).

**DISCUSSION**

The main finding of our study is that the Berlin definition for the clinical diagnosis of ARDS showed a high sensitivity and low specificity for the diagnosis of DAD. DAD was found in fewer than half of the patients with clinical criteria for ARDS, but was more frequent (69%) in patients with severe ARDS who met clinical criteria for ARDS during more than 72 hours.

DAD is the histopathological hallmark of ARDS (8), but specificity is inevitably altered by many other diseases that resemble the clinical picture of ARDS, but are not associated with the same histopathology, such as bacterial or viral pneumonia, diffuse interstitial pneumonia, pulmonary infarction or hemorrhage, lymphangitis, or cancer infiltration. Pneumonia was found in half of patients who met the clinical criteria for ARDS without DAD. Although no clinical criteria allow for the differentiation of the two diagnoses, microscopic analysis of the lungs can easily differentiate pneumonia, characterized by intense neutrophilic infiltration in the intra-alveolar spaces, from ARDS, characterized by typical lesions of hyaline membranes. However,
not all experts participating in the Berlin definition were in complete agreement that DAD is the sole pathologic correlate of ARDS, and some considered pneumonia as compatible with ARDS when clinical criteria are met (14). In our study, DAD or pneumonia was present in 74% of patients with clinical criteria for ARDS and in 88% in those considered as having severe ARDS. By contrast, some patients met clinical criteria for ARDS without any pulmonary lesion at autopsy examination. In this case, we cannot exclude that opacities on chest radiograph were atelectasis. Indeed, it is necessary to inflate the lungs at high pressure before microscopic examination, causing re-expansion of collapsed areas. Moreover, there is a significant interobserver variability in the analysis of chest radiographs (15, 16), which may have led to false-positive interpretation of bilateral opacities. Indeed, chest radiographs could be difficult to interpret, especially in patients with obesity and large pleural effusions that can be misinterpreted as bilateral opacities.

We found that fewer than half of patients who met clinical criteria for ARDS had DAD. However, the proportion of DAD depended on the severity of ARDS, and was more frequent in severe ARDS. The presence of DAD markedly increased in patients who met clinical criteria for ARDS more than 72 hours without further increase for longer durations. Although autopsy was performed after a median duration of 5 days between the onset of ARDS and death, we decided to compare patients who met clinical criteria for ARDS during more than 72 hours with those who met the criteria during less than 72 hours, because the incidence of DAD showed a frank difference after the threshold time. In clinical practice, patients with ARDS are not detected in all cases the first day they met clinical criteria, and 72 hours is the time needed to identify the majority of patients with ARDS (17). Therefore, severe ARDS of more than 72 hours could represent a homogenous group of patients with a high proportion of DAD. However, the absence of hyaline membranes during the first 3 days may be due to a short duration of the process, as hyaline membrane formation may take 2–3 days (8), resulting in underestimation of the true proportion of patients with ARDS with DAD.

Unlike our first study (10), the origin of ARDS had no influence on the proportion of DAD. It has been suggested that pulmonary or extrapulmonary origin of ARDS may influence lung compliance and response to PEEP (18). However, other studies showed that the origin of ARDS has no impact on alveolar recruitment induced by PEEP (19) or mortality (20).

As expected, we observed a change in ventilator settings over time with a marked reduction of tidal volume in patients with any risk factor for ARDS. In 2000, a large randomized controlled study found a reduction of mortality in patients with ARDS ventilated using low tidal volume (11). Some studies have even shown that reduction of tidal volume may prevent the occurrence of ARDS in patients ventilated in the ICU (21, 22). This protective ventilation strategy was accompanied by a lower incidence of DAD and ARDS. In the present study, we show, for the first time to our knowledge, the parallel evolution of the tidal volume and the morphological abnormalities in patients with ARDS.

In agreement with previous literature (23, 24), we found that refractory hypoxemia did not exceed 20% of the causes of death in patients with ARDS. However, refractory hypoxemia was the cause of death in nearly half of the patients with severe ARDS with full life support, suggesting that treatment should focus on improved oxygenation in these patients. Indeed, prone positioning seems effective to improve outcome in the more hypoxic patients (25, 26), and treatments aiming at improving oxygenation could be useful to reduce mortality in severe ARDS. Therefore, severity of ARDS may have an impact on the response to treatment, which should be considered for patient selection in future clinical trials.

One of the limitations of our study is that patients with ARDS were retrospectively identified and classified. However, even prospectively, ARDS is frequently underrecognized by clinicians (27). Moreover, prospective analysis of chest radiographs would not have improved the results. Finally, the retrospective analysis should not alter the classification according to the severity, which depends only on the PaO2/FIO2 ratio. Systematic determination of clinical errors by comparing clinical and pathological diagnoses from clinical autopsies has been our usual practice for more than 20 years, allowing us to apply a standard procedure (28–30). Obviously, clinical autopsy allows the analysis of only patients who died, and, therefore, the patients with the most severe disease. Our main limitation is that histological findings may differ in patients with less severe ARDS.

Sensitivity was higher and specificity was lower using the Berlin definition as compared with our previous work evaluating the
AECC definition (10). There could be several reasons for the discrepancies. First, patients with a PaO2/FiO2 ratio below 201 and 300 mm Hg were considered as having ARDS in the Berlin definition, whereas they were considered as having acute lung injury in the AECC definition (2). Given the low proportion of mild ARDS with DAD, specificity decreases. Second, patients with transient cardiogenic contribution to the formation of pulmonary edema were classified as having ARDS in the Berlin definition, whereas, in the AECC definition, they were classified as having cardiogenic pulmonary edema if pulmonary artery occlusion pressure was above 18 mm Hg. It has recently been shown that high pulmonary artery occlusion pressure could coexist with DAD (5, 6), and we therefore included patients with transient cardiogenic pulmonary edema, although this group may contain a lower proportion of patients with DAD. Third, morphological features of DAD were found less frequently in autopsies from patients with risk factors for ARDS during the second decade than during the first decade, explaining a lower specificity. Fourth, in our previous study (10), a radiographic criterion of “airspace changes in all four quadrants” was used and chest radiographs were reviewed from the patient’s entire ICU stay. By contrast, we employed a radiographic criterion of “bilateral infiltrates” in the current study, as specified in the Berlin definition, and chest radiographs were reviewed only within the 48 hours before death. This highlights the importance of the methodology used to determine the diagnosis of ARDS.

In another study from our group, Ferguson and colleagues (27) found that specificity varied considerably according to the clinical definition used, and specificity of the previous American–European definition was around 50%. In addition, another group has recently found a specificity of only 35% in patients with ARDS due to community acquired pneumonia (31).

It could be argued that specificity of the Berlin definition for ARDS was relatively poor using DAD as the reference standard. However, the Berlin definition allowed the identification of mild ARDS without typical histopathological abnormalities, and severe ARDS characterized by a high proportion of DAD, especially after 3 days of evolution. This population at high risk of mortality could be targeted for future clinical trials.

In conclusion, almost all patients with DAD on autopsy examination met the clinical criteria of the Berlin definition for ARDS, whereas fewer than half of the patients who met clinical criteria for ARDS had DAD. However, the Berlin definition allows the identification of a homogeneous group of patients, including patients with severe ARDS for longer than 72 hours, of which 69% present DAD.

References


