



## Editorial

## Airway Alterations and Diffuse Alveolar Damage in Acute Respiratory Distress Syndrome: Is There Any Association?



### Alteraciones de las vías respiratorias y daño alveolar difuso en el síndrome de distrés respiratorio: ¿existe alguna relación?

 Oriol Roca<sup>a,b,\*</sup>, Marina García-de-Acilu<sup>a</sup>, Tania Soriano-Navarro<sup>c</sup>, Mark J.D. Griffiths<sup>c,d</sup>
<sup>a</sup> Critical Care Department, Hospital Universitari Vall d'Hebron, Institut de Recerca Vall d'Hebron, Barcelona, Spain

<sup>b</sup> Ciber Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

<sup>c</sup> Barts Heart Centre, St Bartholomew's Hospital, London, United Kingdom

<sup>d</sup> Imperial College London, London, United Kingdom

Diffuse alveolar damage (DAD) has been considered the histopathological hallmark for the acute phase of acute respiratory distress syndrome (ARDS). However, ARDS has been defined using clinical criteria.<sup>1</sup> As a result, not all patients with ARDS have DAD and not all patients with DAD have ARDS. To know which ARDS patients present DAD is important as it defines a subphenotype of clinical ARDS that is associated with higher mortality<sup>2</sup> that might respond to different treatment strategies. In addition, as ARDS mimics other entities, to obtain an histological sample of the lung tissue may be also important in order to initiate the appropriate treatment.<sup>3</sup> Unfortunately, to obtain the histological confirmation of DAD in severely hypoxemic ARDS patients is often risky. Indeed, lung biopsy may be only considered in those ARDS cases that do not respond to conventional support measures and who had inconclusive results in all other examinations, such as bronchoalveolar lavage, CT scan, blood samples or specific immunologic analyses. Moreover, it can be also considered in those patients in whom we want to confirm the presence of fibroproliferation and the absence of concomitant infection in order to consider corticosteroid treatment.<sup>4</sup> Therefore, to discovering surrogate markers of DAD may be of interest.

In this sense, some clinical variables have been investigated. However, the diagnostic accuracy of clinical variables in DAD assessment in those patients who meet ARDS criteria is relatively low. Indeed, DAD was only found in the autopsy sample of two-third of the ARDS patients with a PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> <100 mmHg and diffuse opacities involving the 4 quadrants.<sup>5</sup> Furthermore, it is likely that this proportion is be even less in mild to moderate ARDS patients.<sup>6</sup> Another approach for investigating surrogates of DAD is the analysis of different biomarkers. Several biomarkers have

been investigated, either in plasma, in bronchoalveolar lavage<sup>7</sup> or in exhaled breath condensate<sup>8</sup> but none of them have been specific to DAD and, consequently, none of them has been incorporated in the clinical practice.

In the present issue of Archivos de Bronconeumología, Ortiz G, et al.<sup>9</sup> hypothesized that airway alterations may be a good surrogate of DAD in ARDS patients. They argue that airways are more accessible and safer to sample and its analysis may also allow to the discovery of new therapeutic targets. Two different studies have analyzed airway alterations in ARDS patients.<sup>10,11</sup> They describe the presence of epithelial denudation, airway inflammation and increased thickness of small airway walls with deposition of collagen I, fibronectin and versican, mainly localized to the outer wall.<sup>10</sup> They also found a high expression of proinflammatory interleukins in both airway epithelial and inflammatory cells compared with controls.<sup>11</sup> Both studies compared the autopsy findings of ARDS patients with DAD with a control group of non-ventilated and non-smoking patients, who died of non-pulmonary cause and had no previous history of lung disease. Thus, two issues limit the plausibility of this hypothesis: first, the airway changes described were non-specific: and second, there has been no comparison between ARDS patients with DAD with ARDS patients without DAD. Finally, the authors also suggested that, as cryo-transbronchial lung biopsy (CTLB) is less invasive than open-lung biopsy, it might help in the diagnosis of airway pathology by histological analysis in patients with clinical ARDS. Unfortunately, no studies using CTLB have been performed in ARDS patients and, therefore, the incidence of its diagnostic readability and associated complications in these patients remain uncertain.

In summary, to know which ARDS patients present histological DAD may help in providing optimum treatment. However, histological studies in severely hypoxemic patients are difficult to perform, as they are associated with a high risk of complications. Therefore, characterizing surrogate markers of DAD and ARDS in general that can be accessed through less invasive approaches and ana-

\* Corresponding author.

 E-mail addresses: [oroca@vhebron.net](mailto:oroca@vhebron.net), [oriol.roca@vhir.org](mailto:oriol.roca@vhir.org) (O. Roca).

lyzed rapidly, ideally at the bedside, may be a preferable approach. Although airway pathological changes may be associated with DAD, only non-specific changes have been reported and there is a lack of comparison with an appropriate control group, ARDS patients without DAD. Therefore, further studies are warranted to confirm this hypothesis.

## References

- Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526–33.
- Cardinal-Fernandez P, Bajwa EK, Dominguez-Calvo A, Menendez JM, Papazian L, Thompson BT. The presence of diffuse alveolar damage on open lung biopsy is associated with mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Chest*. 2016;149:1155–64.
- Aublanc M, Perinel S, Guerin C. Acute respiratory distress syndrome mimics: the role of lung biopsy. *Curr Opin Crit Care*. 2017;23:24–9.
- Papazian L, Calfee CS, Chiumello D, Luyt CE, Meyer NJ, Sekiguchi H, et al. Diagnostic workup for ARDS patients. *Intensive Care Med*. 2016;42:674–85.
- Thille AW, Penuelas O, Lorente JA, Fernandez-Segoviano P, Rodriguez JM, Aramburu JA, et al. Predictors of diffuse alveolar damage in patients with acute respiratory distress syndrome: a retrospective analysis of clinical autopsies. *Crit Care*. 2017;21:254.
- Thille AW, Esteban A, Fernandez-Segoviano P, Rodriguez JM, Aramburu JA, Penuelas O, et al. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. *Am J Respir Crit Care Med*. 2013;187:761–7.
- Proudfoot AG, Hind M, Griffiths MJ. Biomarkers of acute lung injury: worth their salt? *BMC Med*. 2011;9:132.
- Roca O, Gomez-Olles S, Cruz MJ, Munoz X, Griffiths MJ, Masclans JR. Effects of salbutamol on exhaled breath condensate biomarkers in acute lung injury: prospective analysis. *Crit Care*. 2008;12:R72.
- Ortiz G, Garay M, Capelozzi V, Cardinal-Fernández P. Airway Pathological Alterations Selectively Associated With Acute Respiratory Distress Syndrome and Diffuse Alveolar Damage – Narrative Review. *Arch Bronconeumol*. 2017. Disponible en: <https://doi.org/10.1016/j.arbres.2018.03.006>.
- Morales MM, Pires-Neto RC, Inforsato N, Lancas T, da Silva LF, Saldiva PH, et al. Small airway remodeling in acute respiratory distress syndrome: a study in autopsy lung tissue. *Crit Care*. 2011;15:R4.
- Pires-Neto RC, Morales MM, Lancas T, Inforsato N, Duarte MI, Amato MB, et al. Expression of acute-phase cytokines, surfactant proteins, and epithelial apoptosis in small airways of human acute respiratory distress syndrome. *J Crit Care*. 2013;28:111e9–00000015e.