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Focusing on the alveolar epithelium: Alveolar fluid clearance in diffuse versus focal ARDSAntoine Monsel¹, Carolyn S. Calfee²

¹Multidisciplinary Intensive Care Unit, Department of Anaesthesiology and Critical Care, La Pitié–Salpêtrière Hospital, Assistance Publique–Hôpitaux de Paris, UPMC Université, Paris, France

²Departments of Medicine and Anesthesia, Division of Pulmonary and Critical Care Medicine, University of California San Francisco, San Francisco

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Corresponding author: Antoine Monsel, M.D., Réanimation Polyvalente, Département d'Anesthésie–Réanimation, Groupe Hospitalier Pitié–Salpêtrière, 47–83, boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel: +33 (0)1 42 16 22 51; Fax: +33 (0)1 42 16 22 69. E-mail: antoine.monsel@gmail.com

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Over the past decade, the identification of sub-phenotypes within heterogeneous diseases, such as asthma and cancer, has led to substantial progress directly impacting the therapeutic management of these conditions. In contrast, although the clinical and biological heterogeneity of the acute respiratory distress syndrome (ARDS) has been increasingly recognized, no consensus exists on the optimal approach for distinguishing relevant ARDS sub-phenotypes.

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One approach to untangling the heterogeneity within ARDS has centred on the variability in the syndrome's radiographic appearance. A computerized tomography (CT)-scan-guided method distinguishing different radiographic patterns associated with ARDS was first described in 1998 [1-4]. These initial investigations demonstrated that diffuse (non-focal) ARDS had a lower incidence and lung compliance, worse outcomes, and better response to positive end-expiratory pressure (PEEP), compared to focal ARDS [3]. Several years later, 2 other clinical trials reported that focal and non-focal ARDS had differential responses to recruitment manoeuvres [5] and prone positioning [6] in terms of gas exchange and distribution of aeration. What has remained elusive, however, is evidence that focal and non-focal ARDS differ on biological and physiological levels.

Recently, plasma levels of the receptor for advanced glycation end-products (sRAGE) were reported to be significantly higher in patients with non-focal compared to focal ARDS. sRAGE is an inflammatory mediator highly expressed in alveolar type 1 epithelial cells and released in the context of acute lung injury [7-9]. Furthermore, sRAGE and alveolar fluid clearance (AFC), which reflects the capacity of the alveolar fluid epithelium to remove oedema fluid from the distal lung, have been demonstrated to be inversely correlated in an *ex vivo* human lung preparation [10], and more recently in acid-induced acute lung injury in mice and in patients with ARDS [11]. Thus, a logical next question is whether AFC would also be able to discriminate non-focal from focal ARDS.

In this issue of the *Journal*, Jabaudon et al. [12] present new data supporting the notion that AFC may indeed differ between these CT-scan based sub-phenotypes of ARDS. The authors compared net AFC rates in 30 patients with focal *versus* non-focal ARDS in a secondary analysis of a prospective observational

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single-centre study investigating the role of sRAGE in ARDS. Non-focal and focal CT-scan-based morphotypes were determined according to the well-validated “CT-scan ARDS study group” criteria [1-4]. AFC rates were on average lower in subjects with non-focal ARDS compared to those with focal ARDS (median [interquartile range], 1.5 [0 - 5.5] *versus* 10.3 [4.5 - 15] %/h, $P = 0.01$). The statistical analysis of the receiver-operating characteristic curve yielded a cut-off value of 9%/h with a sensitivity of 86% and a specificity of 96% for discriminating focal from non-focal ARDS. Although the sample size is small and the findings need to be repeated, the results are biologically plausible and add to the weight of literature supporting the concept that focal and non-focal ARDS may represent distinct ARDS subtypes.

The use of AFC as a dynamic functional biomarker of alveolar epithelial injury is unusual in human studies and therefore particularly valuable. Indeed, since AFC reflects the functional status of the alveolar epithelium, it might be viewed as a more functional marker than sRAGE or inflammatory cytokines. The linkage between AFC, the radiographic pattern of ARDS, and sRAGE levels that this group has now demonstrated paints a portrait of a potential ARDS subtype with clinical, physiologic, and biologic dimensions and strong face validity. These results support current and future research aimed at determining whether ARDS contains different endotypes driven by distinct pathophysiological pathways and differential responses to specific therapies.

Aside from this approach based on chest CT, there have been several recent efforts to use data-driven approaches for the identification of subtypes within ARDS [13, 14]. Using a latent class analysis approach combining clinical and biological data from patients from 2 ARDS Network trials, Calfee et al. described two ARDS subtypes, one of which had more severe inflammation, shock, metabolic acidosis and

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poorer clinical outcomes, as well as a differential response to PEEP [13]. Using a similar statistical approach applied to patients with trauma-related ARDS, Reilly et al. identified two categories of ARDS: “early” (< 48 h before presentation) *versus* “late” (> 48 h to 5 days) -onset disease [14]. How the radiologic morphotypes of ARDS identified in the present study relate to the subtypes of ARDS reported in these prior studies remains unknown and potentially intriguing.

While this paper is an important addition to the literature with considerable strengths, it also has certain limitations. Although some important factors impacting AFC, such as corticosteroid and vasopressor use, did not differ between groups, significant differences in PEEP and tidal volume between focal and non-focal ARDS may have significantly confounded the results. Since these factors influence AFC rates [15, 16], it will be important to control or adjust for them in future studies in order to validate the presented results in a larger cohort of patients. In addition, since patients with non-focal ARDS by definition have a greater extent of lung injury, and therefore presumably of lung epithelial disruption, it remains unclear whether AFC truly distinguishes 2 distinct morphotypes or simply reflects the extent of lung epithelial injury. Indeed, a strong relationship between AFC and the severity of lung injury, including degree of histological injury extension, impaired oxygenation, and radiographic infiltrates resolution, has been described [17-20]. Several studies have found that AFC was partially preserved in models of indirect ARDS (e.g., ischaemia-reperfusion model), suggesting that an intact alveolocapillary barrier is associated with preserved AFC [20, 21]. In the current study, 43% of the focal ARDS (*versus* 17% in the non-focal) were caused by extra-pulmonary sepsis (i.e. indirect ARDS), which may therefore have contributed to the differences in AFC between the focal and non-focal groups. Finally, since the authors used a blinded sampling method for

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alveolar protein quantification, focal ARDS patients might have been sampled in areas with relatively preserved epithelial function, leading to over-estimating AFC. Indeed, distribution of lung CT-scan abnormalities (*i.e.*, lung alveolar or interstitial oedema) is diffuse, extensive and homogeneous in non-focal ARDS patients while heterogeneously distributed throughout the lung in focal ARDS patients. The fact that 43% of the focal ARDS group exhibited a maximal AFC level, with a high standard deviation, is interesting but also supports this potential concern.

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At present, measurement of AFC at the bedside, while relatively straightforward and safe, does not have much of a role in clinical practice. Rather than a tool for assigning ARDS morphotypes, which can be easily done with lung ultrasounds (non-invasive, without transferring the patient) [22-30], the capacity of AFC to distinguish focal *versus* non-focal ARDS may be most important in that it supports the existence of distinct pathophysiologic mechanisms underlying the separation into focal and non-focal ARDS. By impairing the resolution of alveolar oedema, the extent of alveolar epithelial injury stands as a major determinant of lung injury.

In summary, the study by Jabaudon et al [12] adds to our understanding of the pathophysiology of ARDS heterogeneity and should inspire further research on the link between impaired AFC (and its highly activated sRAGE signaling pathway counterpart) and lung morphology (focal *versus* non-focal) in patients with ARDS. Future research should focus on whether CT-morphology based ARDS subtypes respond differently to therapies in randomized controlled trials and should investigate biological differences between these subtypes in more detail. Of note, a multicentre randomized controlled trial testing 2 distinct therapeutic regimens based on ARDS morphotypes (focal *versus* non-focal) is underway (LIVE study, NCT02149589).

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These efforts represent important steps towards applying personalized or precision medicine within critical care – a long-awaited and worthy goal.

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