Commentary

KL-6 in acute lung injury: will it leave its mark?

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Abstract

Studies have indicated that measuring biochemical measures of epithelial injury in plasma and alveolar fluid may be useful in predicting outcome in acute lung injury. The present commentary briefly reviews the evidence supporting the use of these biochemical biomarkers of epithelial injury in acute lung injury, and in particular KL-6, as well as their limitations. The article additionally proposes the need for physiological markers of epithelial function to complement current biochemical biomarkers.

In the previous issue of *Critical Care* Nathani and colleagues have assessed KL-6, a specific marker of type 2 alveolar epithelial cell injury, as a biomarker in acute lung injury (ALI) [1]. Biomarkers allow identification of patients at risk of developing disease or can be used as surrogate measures for clinical outcomes. Additionally, measuring biological markers may be a valuable tool in understanding disease pathogenesis. In ALI, the alveolar capillary barrier is disrupted and the alveolar epithelial cell function is critical to the recovery from ALI/acute respiratory distress syndrome (ARDS) [2]. This knowledge provides a rationale for measurement of alveolar epithelial cell injury using surrogate biochemical measures such as KL-6, as a biomarker of ALI.

In the study of Nathani and colleagues, plasma and bronchoalveolar lavage samples were collected following inclusion and on day 4 from 30 ventilated ALI patients, from 12 patients at risk of developing ALI and from 10 nonsmoking volunteers free of respiratory disease The study therefore had the benefit of allowing the investigators to look at KL-6 both in physiological and pathological states. The important findings from the study are that plasma KL-6 levels are increased in patients with ALI, plasma KL-6 correlates with the severity of lung injury and plasma KL-6 is significantly elevated in nonsurvivors compared with survivors. Furthermore bronchoalveolar lavage KL-6 is elevated in patients with ALI and is higher in nonsurvivors. KL-6 did not identify patients at risk of developing ALI. These findings extend the previous data showing KL-6 is elevated in plasma and epithelial lining fluid in ALI [3,4].

In relation to KL-6 in ALI, questions that still remain to be answered include the specificity of the type 2 epithelial cell as the source of KL-6 [5] as well as a need to confirm whether KL-6 elevation reflects epithelial cell injury, regeneration or secretion in response to inflammatory mediators. In addition, mechanical ventilation is known to cause epithelial injury [6], and an important area in which biomarkers may be valuable is in the assessment of ventilator-associated lung injury. Increased surfactant protein D is associated with injurious ventilation strategies [7], and it would be interesting to know the effects of mechanical ventilation on KL-6.

Regardless of these outstanding questions, Nathani and colleagues' work – together with other data showing that elevated surfactant protein D, a type 2 epithelial cell product, is associated with a worse clinical outcome in ALI/ARDS [7] and that the Receptor for Advanced Glycation End-products, an alveolar type 1 epithelial cell-associated protein, is increased in patients with ALI [8] – implicates epithelial cell damage as an important determinant of outcome and implies the potential for alveolar epithelial cell biomarkers to predict outcome in ALI. Further, these data support the central role of epithelial injury in the pathogenesis of ALI.

Notable limitations of all these surrogate biomarkers exist; they do not directly measure epithelial function, and they

ALI = acute lung injury; ARDS = acute respiratory distress syndrome.

require laboratory analysis and therefore cannot be performed by a clinician at the bedside. Additionally, there is no biomarker of epithelial function that reliably identifies patients at risk of ALI who will develop ALI. There is therefore a need to develop additional functional measures of epithelial activity.

One such functional measure that merits further research is nasal potential difference. The resolution of pulmonary oedema from the alveolar space, which is dependent on alveolar fluid clearance, is critical to the recovery from ALI/ARDS. Alveolar fluid clearance depends on active transport of sodium across a functioning alveolar epithelium. Ion transport across the epithelium generates a transepithelial potential difference [9]. Although this cannot be measured at the alveolus, the potential difference can be measured readily across the nasal epithelium. Measuring nasal potential difference is a simple noninvasive measurement easily undertaken repeatedly at the bedside. In an animal model, measurement of nasal potential difference correlated with alveolar fluid clearance [10]. This observation supports the hypothesis that nasal potential difference measurement may be a surrogate marker for alveolar epithelial function. Furthermore, premature infants with pulmonary oedema [11] and patients susceptible to high-altitude pulmonary oedema [12] have reduced nasal transepithelial sodium resorption, as measured by the baseline nasal potential difference, indicating that nasal potential difference measurement may be able to identify patients at risk of developing ALI.

Although further work validating such functional measures of epithelial activity is required, it is probable that as well as biochemical measures such as KL-6, as demonstrated by Nathani and colleagues, future biomarkers in ALI will combine both biochemical and functional measures.

Competing interests

The authors declare that they have no competing interests.

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