EDITORIAL

Elastase and its physiological inhibitors in ARDS: what decides between inflammatory storm or dead calm?

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The mechanisms involved in the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have been clarified to a certain extent over the last 10 yrs. A number of serious underlying diseases such as trauma, severe pneumonia or sepsis initiate a cascade of cellular and biochemical inflammatory reactions within the lung parenchyma, leading to a marked increase in capillary permeability, pulmonary oedema and severe gas exchange disturbances. Neutrophil attraction and activation by mediators such as cytokines and their release of elastase and oxygen radicals are hallmarks of ARDS [1–4].

Neutrophil elastase is involved in several types of lung damage in humans, including some forms of emphysema, chronic bronchitis, cystic fibrosis and ARDS. An imbalance between the enzyme elastase and its natural inhibitors seems to play a key role in these diseases [5–7]. A “physiologic release” of antiproteinas in ARDS and subsequent neutralization of elastase is also well described [4, 8]. In addition, experimental observations suggest that treatment with elastase inhibitors reduces lung injury caused by endotoxin [9].

The data reported by Salonen et al. [10] in this issue indicate that there was an increase of elastase inhibitors in the bronchoalveolar lavage (BAL) fluid of patients at risk of developing ARDS, which appears to contradict the important role played by leukocyte elastase in this syndrome. Do these data merely reflect an excessive autoregulatory reaction? Is the BAL level of antiproteinases directly related to the amount of elastase liberated a short time before? Can an overshooting neutralization of elastase by itself cause tissue damage?

At this time, we do not have answers to all these questions; even worse, we do not really understand how the delicate balance between pro- and anti-inflammatory forces is regulated, nor how the beneficial and detrimental activities of the neutrophils are titrated in situations such as severe infection, sepsis or ARDS. In addition, the relevance of local versus systemic levels of elastase, its inhibitors and other mediators of lung injury and remodelling remain to be elucidated [4, 11, 12].

The incidence of ARDS after trauma or sepsis varies widely in the reported series, but is never >50%. This suggests that in a major proportion of the patients, the inflammatory cascade does not lead to severe tissue injury and/or the pulmonary parenchymal reaction and dysfunction is aborted or prevented. The balance between elastases and antielastases, and the characteristics of their release, binding and inactivation are certainly of primordial importance for whether or not severe tissue injury develops. However, we are still far away from a good understanding of these mechanisms.

The study of Salonen et al. [10] helps to push our understanding a small step further. The conclusion drawn by the authors can certainly be supported by the presence in the BAL of increased levels of antiproteinas in the early phases of ARDS development, whereas it is more difficult to accept that this finding may offer therapeutic potential in these patients for reducing morbidity and mortality. However, the conclusions of the present work from Scotland are clearly supported by another clinical study from Southern England, suggesting that together with surfactant administration in ARDS "antiprotease therapy may improve therapeutic prospects" [13].

Despite these encouraging signals, more unravelling of the pathophysiology of acute respiratory distress syndrome must be achieved before these findings can result in therapeutic implications.

References