Commentary
Nebulised heparin: a new approach to the treatment of acute lung injury?

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Abstract

The administration of heparin by nebulisation has been proposed for the 'local' treatment of pulmonary coagulation disturbances in acute lung injury (ALI). Alveolar and lung micro-vascular fibrin accumulation and breakdown inhibition indeed play a central role in the development and clinical course of this disease. Preclinical studies provide some evidence of the beneficial effects of heparin inhalation in several animal models of ALI. Clinical investigations are sparse, and trials such as the one presented by Dixon and colleagues in a recent issue of *Critical Care* are welcome as they provide insight into the possible clinical use of nebulised heparin in this situation. This phase 1 trial involved 16 patients with early ALI, and showed the feasibility of the approach. In addition, non-significant changes in respiratory functions and systemic anti-coagulant effects were documented with the four doses tested. The study of Dixon and colleagues adds to data that helps pave the way towards a possible clinical use of heparin by nebulisation in ALI. It remains to be clarified in which clinical situations, at what time points and with which dosages the best chances exist for a beneficial effect on the prognosis of these patients.

The inhalation route has been used for the administration of drugs for many years, mainly in diseases localized in the airways, such as asthma or chronic obstructive lung disease, but also in certain forms of severe bronchopulmonary infections. Another disease for which such an approach has been discussed is acute lung injury (ALI), where direct application of substances to altered lung tissue could represent a valid alternative to systemic administration.

Barry Dixon and colleagues [1] have examined the effects of heparin applied by nebulisation in this disease. In a pilot study involving 16 patients, the effects of 4 different doses of inhaled heparin on respiratory function and systemic coagulation factors, as well as its products in bronchoalveolar lavage fluid (BAL), were explored. The results indicate that this therapy did not cause significant changes in the ratio of arterial oxygen partial pressure (PaO_2) to inspired oxygen fraction (FiO_2), dead space or compliance. However, a trend for an increasing systemic anticoagulant effect with higher doses was observed.

The potential of airways and alveoli to absorb particles and chemical substances is impressive. The layer of liquid and surfactant covering the epithelial cells is continuous and offers relatively uniform diffusion possibilities. Inhaled particles can be observed submersed in the aqueous lining layer and adjacent to epithelial cells [2]. This allows interaction with these cells as well as diffusion through them into interstitial space and vascular and alveolar structures.

ALI seems an appropriate situation in which to consider application of an anticoagulant substance by the tracheo-bronchial route. This disease is characterized by typical pulmonary parenchymal changes, including marked inflammation, interstitial edema, microvascular thrombosis, alveolar fibrin deposition and fluid accumulation [3]. It has been shown, on one hand, that pulmonary inflammation can cause local disturbances in fibrin turnover; and on the other hand, it is known that an intra-alveolar pro-coagulant state with increased fibrin deposition and limited breakdown may enhance inflammatory changes [4-6]. The role of platelets and leukocytes, activated by these coagulation disorders, must also be stressed. Given the extensive crosstalk between coagulation and inflammation, targeting pulmonary coagulo-pathy may influence the local inflammatory response and, thereby, the clinical course of ALI [6]. As suggested by a number of experimental and clinical studies, heparin has anti-coagulant and fibrinolytic properties as well as anti-inflammatory effects. Given by nebulisation, this substance had positive effects in animal models of ALI or lung fibrosis [7,8].

ALI = acute lung injury.

The translation of a potentially beneficial effect of inhaled heparin in experimental models of ALI to clinical practice has not yet been achieved; important additional work remains to be done. The following questions need to be answered. As the pro-coagulant state in the alveolar space begins in the early phases of ALI, how can it be assessed in order to initiate heparin administration as rapidly as necessary? How can dosage of the drug be titrated to achieve maximal local effects without the risk of systemic complications? What is the adequate duration of this therapy? Does the underlying cause of ALI make any difference with regard to this approach? Ultimately, randomized controlled trials will provide the data necessary to determine its clinical utility.

ALI represents a complex syndrome with different possible causes and origins, but also involves patients with complex conditions: 'standard' care has to be defined in detail in such situations, and rigorous control of physiological variables as well as therapeutic modalities is of the outmost importance [9]. The use of 'treatment bundles' could be a further necessary step in the direction of optimal patient management in this disease [10].

Competing interests
The author declares that he has no competing interests.

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