

Commentary

Improving survival by increasing lung edema clearance: is airspace delivery of dopamine a solution?

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See related research by Chamorro-Marín *et al.*, <http://ccforum.com/content/12/2/R39>

Abstract

In this issue of *Critical Care* Chamorro-Marín and coworkers provide new evidence that dopamine instilled into airspaces is beneficial in a rat model of ventilator-induced lung injury. This study is important because it is the first to explore the effects of dopamine on survival, albeit short term. The delivery of dopamine into the airspaces *in vivo* is also novel and builds upon previous studies describing the mechanisms by which dopamine exerts its effect by upregulating active Na⁺ transport in the lungs. Dopamine appears to increase active Na⁺ transport via activation of amiloride-sensitive sodium channels and the basolateral Na⁺/K⁺-ATPase within minutes, and it has been shown to be effective in normal lungs and several models of lung injury. This information is relevant to current clinical trials exploring the effects of alveolar fluid clearance stimulation in patients with acute lung injury.

In this issue of *Critical Care* Chamorro-Marín and coworkers [1] reported a significant decrease in short-term ventilator-induced lung injury (VILI)-related mortality by intratracheal administration of dopamine in rats subjected to injurious (high tidal volume) mechanical ventilation. This finding is interesting and has potentially relevant implications for mechanically ventilated patients with acute lung injury.

VILI occurs when the lung tissue is disrupted by high tidal volumes during mechanical ventilation, leading to pulmonary edema and hypoxemia [2]. The lung injury and edema formation were proposed to be due to activation of intracellular signals that initiate/amplify an injurious cascade that leads to systemic inflammation and dysfunction of other organs [2]. Many strategies have been tested with the aim being to decrease the deleterious effects of VILI. The one approach with more acknowledged success was that evaluated in the the US National Institutes of Health-sponsored ARDSnet study, which showed that ventilating patients with acute respiratory distress syndrome with a low tidal volume strategy

(about 6 ml/kg) decreased mortality in this patient population. Other approaches such as high levels of positive end-expiratory pressure, prone positioning, and recruitment maneuvers appear to improve hypoxemia but have not yet been shown to reduce mortality [3]. Despite the incorporation of these approaches into clinical practice, the incidence of VILI and mortality in patients with pulmonary edema remains high.

In their study in rats, Chamorro-Marín and coworkers [1] found that administration of dopamine in airspaces exposed to injurious (high tidal volume) mechanical ventilation resulted in lower lung wet weight/dry weight ratio (a gravimetric estimate of pulmonary edema) and improved survival in the dopamine-treated group. As such, the study provides interesting and novel information. For example, the use of very high levels of tidal volume which cause lung injury may suggest that the dopamine instillation strategy could be of benefit, particularly in patients who cannot tolerate low tidal volume, as is the case for a small proportion of patients who require ventilation with injuriously high tidal volumes. Also, as shown in Table 2 of the report by Chamorro-Marín and coworkers [1], dopamine instilled into rat airspaces did not appear to cause deleterious hemodynamic effects, as are sometimes observed during systemic administration of dopamine, particularly at higher doses. A limitation of the study is that although relevant, the research focuses on a very short period of time and further studies would be of benefit to validate these interesting observations. As mentioned by the investigators, research in larger animals, reflecting the situation in patients to a greater extent, would be of significant interest.

An important question highlighted by this research is why and how does dopamine exert its effects in the lungs of animal models (and hopefully in patients)? Dopamine has been

VILI = ventilator-induced lung injury.

reported to accelerate clearance of lung edema in normal and VILI lung models via activation of D₁ and D₂ receptors [4-6]. These reports demonstrated that activating dopaminergic D₁ receptors increases, within minutes, Na⁺/K⁺-ATPase activity by promoting the recruitment of Na⁺ pump proteins from intracellular endosomal compartments into the plasma membrane of alveolar epithelial cells via specific signaling pathways that involve cell microtubules and actin cell cytoskeleton [7-9]. Dopamine has been also shown to activate amiloride-sensitive Na⁺ channels in alveolar epithelial type I cells, which cover most of the alveolar epithelial surface area [10].

Interestingly, activating dopaminergic D₂ receptors has a different effect on the Na⁺/K⁺-ATPase, which includes stimulation of mitogen-activated kinase ERK1/2 (extracellular signal-regulated kinase-1/2), leading to increased transcription/translation of the Na⁺/K⁺-ATPase proteins by 24 hours [6]. It thus appears that dopamine, by increasing initially the Na⁺/K⁺-ATPase protein abundance at the plasma membrane and later by increasing protein translation, leads to higher Na⁺/K⁺-ATPase activity and hence increased edema clearance.

The other important issue is that dopamine in this and in some previous studies was delivered intratracheally, which decreases the potentially confounding systemic effects, thus offering a therapeutic alternative. The more localized approach to delivering β-adrenergic agonists to lung epithelium has been reported to be beneficial in patients with pulmonary edema [11] and is now the focus of large multicenter clinical trials. The study by Chamorro-Marin and coworkers [1] provides further evidence, albeit in an animal model, that direct therapy with yet another inexpensive drug (dopamine) delivered to the lungs can be of benefit in terms of improving oxygenation and short-term survival.

In summary, Chamorro-Marin and coworkers [1] present interesting data in an animal model of lung injury that suggest a beneficial effect of dopamine delivered directly to lung epithelium, which may be applied as an adjuvant measure to counteract the deleterious effects of VILI; those investigators also provide valuable insight into the pathophysiology of VILI. Delivering pharmacologic agents directly to the bronchial and alveolar epithelium may become a valid therapeutic strategy for treating patients with pulmonary edema and avoiding systemic effects of compounds that are relatively inexpensive and with which physicians are quite familiar.

Competing interests

The author declares that they have no competing interests.

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