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EDITORIAL

Almitrine and NO in acute respiratory distress syndrome: two pieces of the same puzzle?

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In the present issue of the *European Respiratory Journal*, PAPAZIAN *et al.* [1] demonstrate that the intravenous administration of almitrine together with the inhalation of a low dose of NO (10 parts per million (ppm)) to 41 patients with acute respiratory distress syndrome (ARDS) results in a dramatic improvement in arterial oxygenation: as a mean, a 100% increase in oxygen tension in arterial blood (P_{a,O_2}/ inspiratory oxygen fraction (F_{I,O_2}) ratio was observed when both therapies were combined. This impressive result confirms seven previously published studies [2–8] demonstrating that the combination of intravenous almitrine and inhaled NO is very effective for improving arterial oxygenation at the early phase of ARDS.

By different mechanisms, both drugs improve P_{a,O_2} by redistributing pulmonary blood flow from nonventilated towards ventilated lung areas. Inhaled NO relieves the constriction of pulmonary vessels perfusing normally- and poorly aerated lung areas. In ARDS, where nonventilated lung areas predominate over poorly-ventilated lung areas, P_{a,O_2} increases whereas pulmonary artery pressure decreases [7, 9]. In chronic obstructive pulmonary disease (COPD), where poorly-aerated lung areas predominate over nonventilated lung areas, pulmonary artery pressure and P_{a,O_2} may both decrease because NO reverses hypoxic pulmonary vasoconstriction and increases pulmonary blood flow towards low ventilation/perfusion ratio (V'/Q') regions [10]. Almitrine is a selective pulmonary vasoconstrictor that at doses <5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ reinforces hypoxic pulmonary vasoconstriction in poorly- and non-ventilated lung regions. The resulting effect is a redistribution of pulmonary blood flow towards normally-ventilated lung regions leading to a decrease in pulmonary shunt and an increase in arterial oxygenation.

True pulmonary shunt and low (V'/Q') regions are coexisting in the lungs of patients with ARDS and inhaled NO may have its beneficial effect on P_{a,O_2} limited by the existence of poorly-ventilated lung regions in which it deteriorates regional oxygenation by inhibiting hypoxic pulmonary vasoconstriction. Almitrine could specifically meet this limitation by locally re-establishing some degree of vasoconstriction. As a matter of fact, there is a strong rationale for combining almitrine and NO and it is not surprising that all human studies performed in patients with ARDS found that NO and almitrine add their effects for improving arterial oxygenation.

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One interesting result of the study by PAPAZIAN *et al.* [1] is the lack of response to almitrine in patients receiving intravenous noradrenalin for septic shock. This contrasts with the results of GALLART *et al.* [7] who found that patients with septic shock receiving noradrenalin respond to almitrine by an increase in P_{a,O_2} of the same magnitude as the one observed in patients without septic shock. In addition, GALLART *et al.* [7] also found that a lower dose of almitrine is required in patients receiving noradrenalin for obtaining the plateau effect on arterial oxygenation (2 *versus* 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Why these conflicting results? The explanation probably resides in the differences in the basal pulmonary artery pressure measured in the patients of each study: in the study by PAPAZIAN *et al.* [1], the mean pulmonary artery pressure of patients receiving noradrenalin was 24±1 mmHg (mean±SEM) before almitrine administration whereas it was 22±3 mmHg in the patients of the study by GALLARTS *et al.* [7]. Since pulmonary vascular resistance was increased in the same proportion in the two studies (5.6 $U \cdot m^{-2}$), pulmonary blood flow was much higher in the patients from the study by PAPAZIAN *et al.* [1]. It can therefore be suspected that almitrine-induced vasoconstriction is inhibited by the presence of a high pulmonary blood flow. Further studies are required to confirm this hypothesis.

Almitrine is available in France for patients with COPD and is increasingly used in intensive care units to reverse severe hypoxaemia resulting from ARDS. Doses around 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and ranging 1–16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ are administered for periods of 2–3 days at the early phase of ARDS. The pharmacological tolerance seems to be good: several hundred critically ill patients have been treated and only a few side effects have been reported [5, 11]. However, three potential issues concerning almitrine's toxicity should be outlined. At doses >5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, almitrine constricts the entire pulmonary circulation [12] and induces a significant rise in pulmonary artery pressure that represents an increased afterload for the right ventricle [1–9]. GALLART *et al.* [7] have demonstrated that in patients with ARDS, four-fold lower doses allow the same improvement in arterial oxygenation without inducing a marked rise in pulmonary artery pressure. As a consequence, the doses that can be recommended today are between 2 and 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and are not usually associated with a marked rise in pulmonary artery pressure. Another potential issue is the neurological toxicity of almitrine. Polyneuropathies associated with long term almitrine administration to patients with COPD (100–200 $mg \cdot day^{-1}$ for several months) were reported in the mid 1980s [12, 13]. A prospective randomized study has

shown that neurological toxicity can be prevented by halving the daily dose (5–100 $mg \cdot day^{-1}$ for period as long as 9 months) [14]. In critically ill patients, there is no published study reporting peripheral neuropathy following the administration of almitrine at the early phase of ARDS. However, it may be difficult to distinguish polyneuropathies related to sepsis, muscle relaxants, corticosteroids and almitrine. A last issue concerning the toxicity of almitrine is its potential for inducing lactate accumulation. B′CHIR *et al.* [5] have reported in 25 patients with focal lung lesions and receiving almitrine in doses ranging 2–8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, a sub-group of 8 patients in whom a significant increase in plasma lactate was observed 24 h following the administration of the drug. In constrast, no increase in lactate concentrations was found by GALLART *et al.* [7] in 17 patients receiving almitrine at doses ranging 2–16 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Unless additional studies comparing the change of plasma lactate between patients receiving and not receiving almitrine rule out the risk of lactate accumulation, daily monitoring of lactate concentration is recommended in patients with ARDS treated by almitrine. The drug should be interrupted if plasma lactate increases.

From the existing literature, the combination of inhaled NO and intravenous almitrine appears today as an attractive therapeutic option for reversing severe impairment of arterial oxygenation at the early phase of acute respiratory distress syndrome. Its long-term effects on arterial oxygenation, outcome and duration of mechanical ventilation are not known and remain to be evaluated by randomized multicentre studies.

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