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EDITORIAL

U. Kaisers
R. Rossaint

Nitric oxide in partial liquid ventilation: better matching ventilation to perfusion in ARDS?

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U. Kaisers · R. Rossaint (✉)
Klinik für Anästhesiologie und Operative Intensivmedizin,
Virchow-Klinikum der Humboldt-Universität zu Berlin,
Augustenburger Platz 1, D-13353 Berlin, Germany,
FAX: +49 (30) 4505 1900

Since the first clinical description of the acute respiratory distress syndrome (ARDS) more than 25 years ago, the syndrome has remained a fatal condition in almost 50% of the patients [1]. Despite the introduction of modified techniques of ventilatory support aiming at lower tidal volumes and airway pressures, additional types of pharmacological treatment including surfactant replacement and the introduction of extracorporal lung assist into clinical practice, intensivists continue to seek new approaches in the treatment of ARDS. During the last few years, two promising strategies have been under intense scrutiny, both experimentally and clinically: the inhalation of nitric oxide (NO) and partial liquid ventilation with perfluorochemicals.

In severe ARDS, the admixture of low concentrations of NO into the inspiratory gas induces selective vasodilatation of ventilated lung areas, causing a decrease in pulmonary artery pressure as well as a redistribution of intrapulmonary blood flow towards these well ventilated lung regions which results in an increase in arterial partial pressure of oxygen (PaO_2) [2, 3]. Partial liquid ventilation, also known as "perfluorocarbon-associated gas exchange" [4], presents a new way to assist ventilation by employing a conventional ventilator to deliver gas tidal volumes into a lung with liquid functional residual capacity. Animal studies and preliminary clinical investigations applying this technique in premature infants as well as in adult ARDS have demonstrated an increase in arterial oxygenation and lung compliance [5, 6].

In this issue of Intensive Care Medicine, Dr. Houmes and colleagues [7] describe the combined use of partial liquid ventilation and inhalation of NO in an animal model of acute lung injury. In their study, doses of more than 10 ml/kg of perflubron (perfluorooctyl bromide) resulted in a significant reduction in intrapulmonary shunt and consequently an increase in PaO_2. The additional administration of four different concentrations of inhaled NO further augmented arterial oxygenation and decreased pulmonary artery pressure. Houmes et al. outlined distinct "on/off" effects of NO in this setting, suggesting no storage of NO in perflubron. Moreover, the authors did not identify any short-term adverse effects of the combined treatment in experimental lung injury. Their encouraging results propose a cumulative efficacy of both techniques and, therefore, their study represents a potentially important advance in the evolution of novel therapeutic concepts for the treatment of respiratory failure. Realizing that most probably no single therapeutic measure will by itself improve outcome in human ARDS, it is common practice to use a whole bundle of procedures such as positive end-expiratory pressure, prone position, or inhalation of NO. Going along with this strategy, it appears to be logical to combine NO inhalation and partial liquid ventilation. Moreover, joining the two techniques might eventually allow a reduction of either the volumes of perfluorocarbons or the concentrations of inhaled NO required to provide adequate gas exchange and pulmonary artery pressure in acute lung injury.

However, some reservations must be noted. Since respiratory gases are easily dissolved in perfluorochemicals, one could expect a certain solubility of NO in perflubron. Unfortunately, there is, as yet, no data available on the amount of NO dissolved in the vapor and

liquid phase of perfluorocarbons. Moreover, the reactions that occur during the solution decomposition of NO in oxygenated perfluorochemicals remain unclear. Considering NO as an intermediate and unstable molecule which easily exists in different redox states [8], it could be presumed that toxic compounds are generated when gaseous NO is combined with oxygenated perfluorochemicals in vivo. Prior to a prospective clinical application, these issues must be clarified by further investigations.

At present, the mechanism responsible for the cumulative effects of NO in the setting of partial liquid ventilation remain speculative. Due to the high density of perfluorocarbons – twice as high as water, intrapulmonary distribution of the liquid is inhomogeneous and follows the gravitational gradient, preferentially pooling in dependent alveoli. Since significant amounts of oxygen and carbon dioxide are dissolved in perfluorocarbons, gas exchange might take place in these liquid-filled alveoli as well. Furthermore, perfluorochemicals have high spreading coefficients and remarkably low surface tensions. In non-dependent, ventilated lung regions, thin layers of the compounds will reduce the surface tension at liquid-gas interfaces and will thereby improve lung mechanics. It has been suggested that the beneficial effects of partial liquid ventilation on gas exchange are partly attributable to the filling and distending of alveoli with a non-compressible fluid, thereby reopening air spaces and preventing them from end-expiratory collapse [9]. In ARDS, this might be especially true in dependent zones of the lung, where the expanded lung weight causes airway closure and alveolar collapse along the vertical axis of the thorax, concentrating compression atelectasis in these dependent regions [10]. However, the same gravitational force which provides the recruitment of dependent alveoli may reduce pulmonary arterial blood flow to these areas, redirecting blood flow towards non-dependent lung regions. In this scenario, the admixture of NO might selectively induce the vasodilatation of pulmonary vessels predominantly receiving blood flow from non-dependent, ventilated alveoli which are stabilized by the surface tension-reducing properties of perfluorocarbons. In the setting of a combined application, NO might therefore be mainly effective in the air-filled compartment of the injured lung. This is supported by the work of Houmes and colleagues [7], demonstrating a sharp "on/off" effect of inhaled NO when added to partial liquid ventilation, suggesting similar kinetics of NO in the perflubron-filled lung compared to conventional mechanical ventilation.

Recent concepts in the treatment of human ARDS primarily involve supportive measures aimed at maintaining gas exchange, organ perfusion and aerobic metabolism while the acute lung injury resolves [11]. The inhalation of NO combined with partial liquid ventilation might serve as a ventilatory technique to provide acceptable gas exchange and lower pulmonary arterial hypertension in severe lung injury. However, additional animal studies on this new concept are required to determine NO/liquid solubility, ascertain non-toxicity and establish prolonged effectiveness.

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