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Short Communication
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Nitric Oxide to Treat ARDS by a Mobile NO Generator

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is a major medical emergency requesting acute therapeutic intervention. Here we report that Nitric Oxide (NO) gas attenuates ARDS in mice. Using a novel portable NO generator we found that NO at 20 ppm attenuates endotoxin (LPS) induced neutrophil recruitment lung alveolar epithelial damage reduced inflammatory cytokines, neutrophil. Therefore, the data suggest that the use of a portable NO generator may be considered as an interesting therapeutic possibility for patients with severe ARDS.

Keywords: ARDS; Endotoxin; Nitric oxide; NO portable generator

Short Communication

Acute Respiratory Distress Syndrome (ARDS) represents a medical urgency with airway epithelia injury and acute pneumonitis and may be caused by pathogens such as bacteria and virus including coronavirus infection (SARS-CoV-2) [1]. A common feature in ARDS patients is lung hyper-inflammation with an excessive release of inflammatory mediators including cytokines known as cytokine storm (Fajgenbaum DC, NJEM 2020) which untreated may lead to respiratory failure. The optimal management of ARDS patients is complex and the efficacy and safety of therapeutic strategies is regularly reviewed [2]. The airway exposure by endotoxins from Gram-negative bacteria induces an Acute Respiratory Distress Syndrome (ARDS) with disruption of the epithelial barrier, neutrophil infiltration and accumulation of inflammatory enriched-mediators [3].

Nitric Oxide (NO) is known to have anti-inflammatory properties with many other functions such as anti-microbial and regulation of the pulmonary vascular function [4-6].

To test the effect of NO we exposed C57BL/6 mice in a chamber to NO gas for 6 h using the portable generator INJECT+MATIC TAS Plus generator (www.injectmatic.com) as reported before [7,8]. After LPS challenge at 1 μg by intranasal route, mice were exposed immediately to continuous NO at 20 ppm in a plexiglass chamber. We found at 6 h reduced recruitment of neutrophils, cytokine releases such IL-1β, IL-6 and TNF and conferred a significant protection from alveolar epithelial damage (Figure 1). Therefore, NO has a protective effect on acute LPS induced lung injury and inflammation.

With the recent outbreak of COVID-19, inhaled NO has been proposed as an interventional rescue therapy [9]. Clinical studies are going to define the efficacy of inhaled NO in COVID-19. Two studies with a small group of patients in intensive care units under ventilation did not showed improvement with short NO treatment (15 min to 30 min) [10,11]. Large studies should define if NO can be effective as emergency therapy for COVID-19 and better determine the group of patients that can benefit of this therapy.

Comment

Comment on NO generator INJECT+MATIC TAS Plus has been recently described to be used for the treatment of neonatal hypertension [7,8]. This NO generator is an electro-pneumatic device enriching atmospheric air in air containing NO without limitation of gas production. Pre-clinical studies carried on three different piglet models of hypertension have demonstrated its safety and therapeutic efficacy. Clinical trials have shown that NO at 20 ppm can be used to treat neonatal hypertension. The amount of NO delivered by the TAS Plus device can be easily regulated and monitored as previously described [7]. Considering the broad range of activities of NO, we asked if inhaled NO can attenuate ARDS in mice. Here, we exposed mice to NO at concentration of 20 ppm in a Plexiglas chamber during 6 h and compared to those maintained in the air ambient following

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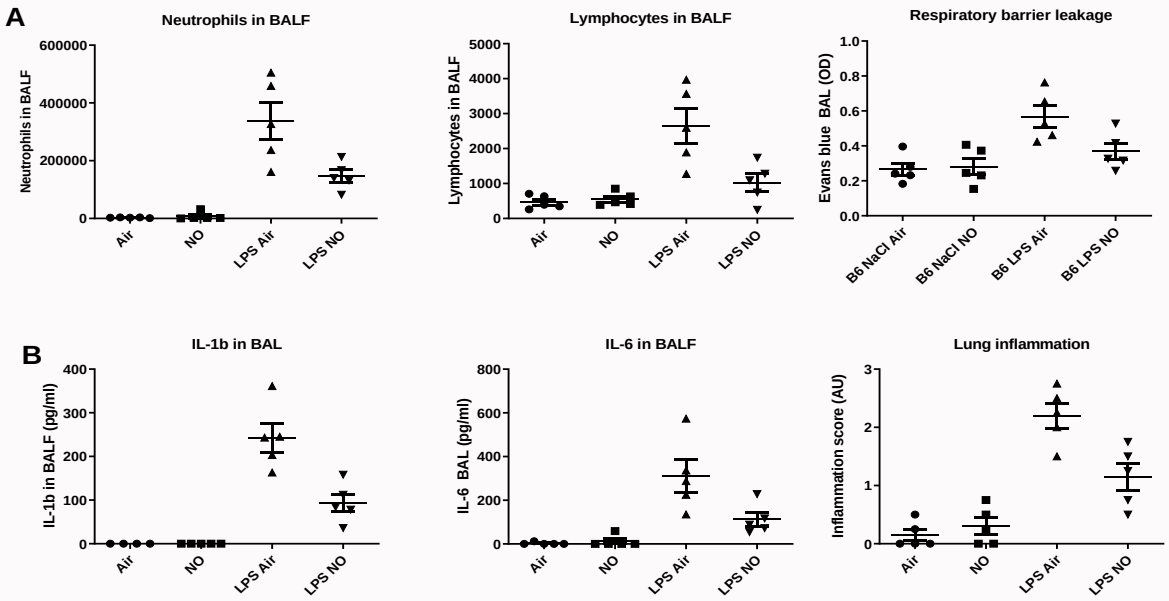

Figure 1: LPS induced inflammatory cell recruitment in BALF and integrity of respiratory barrier, cytokines and alveolitis. A) Neutrophils and lymphocytes counts and Evans Blue leakage in BALF. B) IL-1β and IL-6 levels in BALF and alveolitis score in lung by microscopy. Groups of 5 female mice were administered LPS (1 µg) by the intranasal route and followed by NO exposure at 20 ppm for 6 h and BALF cells and BALF were analyzed at 6 h. Data are representative of two independent experiments and expressed as individual spots and mean ± SD, *p<0.05.

LPS or saline administration.

Conclusion

In conclusion, our previous studies showed a beneficial effect of NO in clinical studies to treat neonate pulmonary hypertension using the low-cost and portable device generating NO. Here we show that the novel NO generator attenuates LPS-induced ARDS pulmonary injury and inflammation in mice. Thus we anticipate a major benefit for a broader range of patients with in ARDS or other inflammatory lung disease by NO therapy using a portable NO generator in the future.

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