Correspondence

Innate Immune Dysfunction in RSV: What Is the Role of Ventilation?

I read with interest the article by Mella et al [1]. The authors observed that infants with severe respiratory syncytial virus (RSV) bronchiolitis had increased plasma cytokine concentrations and yet impaired innate immunity cytokine production capacity. More specifically, plasma interleukin (IL)-6, IL-8, and IL-10 concentrations were modestly but significantly increased in RSV-infected patients compared with controls, with no differences between pediatric intensive care unit (PICU) and floor patients. However, the authors observed that ex vivo lipopolysaccharide-induced production of tumor necrosis factor-alpha (TNF-α), IL-6, and IL-8 was significantly decreased only in PICU patients compared with floor patients and healthy controls. No differences were found in cytokine production capacity between floor patients and healthy controls. Finally, female sex and PICU admission were identified as independent predictors for decreased production capacity of TNF-α and IL-8 in multivariate analysis.

Interestingly, among PICU patients, 75% required noninvasive ventilation for a median of 2.3 days and 20% required invasive ventilation for a median of 4.5 days. Although briefly discussed by the authors, the effect of mechanical ventilation on peripheral immune depression remains unclear. We previously demonstrated in a prospective study in healthy infants without preexisting lung pathology that brief exposure to mechanical ventilation resulted in a significant change in the functional capacity of peripheral blood leukocytes [2]. Although we observed a proinflammatory response in the tracheal aspirates after 2 hours of mechanical ventilation, the functional capacity of peripheral blood leukocytes to produce interferon-gamma (IFN-γ), TNF-α, and IL-6 was significantly decreased. This was accompanied by a significant decrease in the killing capacity of natural killer cells. The observed change in Th1/Th2 balance in favor of Th2 cytokine activity may be a systemic adaptation to the proinflammatory milieu in the lung. These observations of ventilator-induced peripheral immune suppression were later confirmed in studies in healthy rats [3]. In these studies, we observed that the degree of peripheral immunosuppression was dependent on the mode of ventilation. For example, IFN-γ production was significantly lower in rats ventilated with high-positive inspiratory pressure and zero-positive end-expiratory pressure (PEEP) compared with low-positive inspiratory pressure and PEEP.

These observations clearly show that mechanical ventilation alone is capable of inducing peripheral immunosuppression. It is possible that this effect is more significant in the presence of underlying lung pathology, for example, RSV, necessitating mechanical ventilation. It is well known that in the presence of underlying lung pathology, the effects of ventilator-induced lung injury, that is, a double-hit exposure, are more harmful than after a single hit [4]. This results in more pulmonary inflammation and, as a consequence, more peripheral immunosuppression. These observations are in accordance with the studies of Bont et al [5]. On the other hand, one may argue that most patients in the study of Mella et al [1] received noninvasive ventilation. Indeed, to date no studies have examined the effect of noninvasive mechanical ventilation on peripheral immune function. However, since we have shown that only 2 hours of mild mechanical ventilation resulted in peripheral immunosuppression, the effect of noninvasive ventilation for a longer period of time on peripheral immunosuppression cannot be ruled out. Therefore, before conclusions can be drawn, it may be necessary to first delineate more precisely the effects of noninvasive ventilation on peripheral immunosuppression, for example, in infants with healthy lungs or in an animal model. This may help to elucidate if innate immune dysfunction is, indeed, associated with enhanced disease severity in infants with severe RSV bronchiolitis or if this observation is, in part, the effect of exposure to ventilation resulting in enhanced immunosuppression.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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Frans B. Plötz
Department of Pediatrics, Tergooi Hospitals, The Netherlands

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