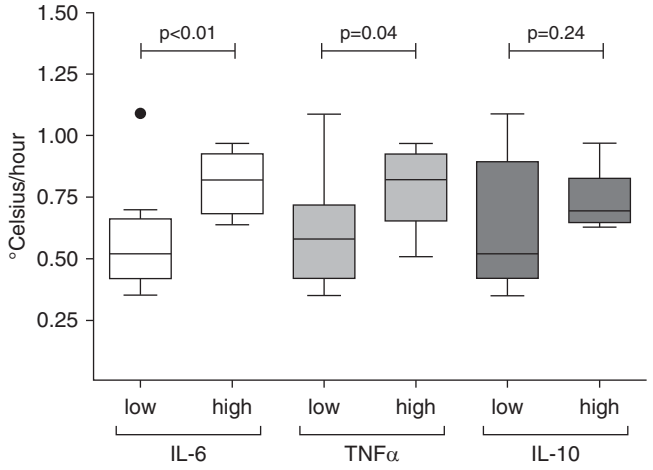

Figure 1. Slope of the temperature increase ($Temp_{slope}$) after endotoxin administration for subjects with low and high peak levels of IL-6, TNFα (tumor necrosis factor α), and IL-10. Data are presented as box-and-whisker plots (Tukey).

an immunological basis for the hypothesis of Bhavani and colleagues, who state that hyperthermia may be the result of a more proinflammatory phenotype, whereas a less pronounced immune response might relate to a lower (or absent) temperature increase. In view of the more favorable prognosis of hyperthermic patients in whom temperature swiftly increases and quickly resolves, a more pronounced but adequately balanced proinflammatory response is of apparent benefit to the host. This further elucidates why dozens of trials using immunosuppressive agents failed to improve sepsis outcome and stresses the need for therapies aimed at maintaining or restoring a well-functioning immune system. ■

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Reply to Leijte *et al.*

From the Authors:

We thank Dr. Leijte, Dr. Kox, and Dr. Pickkers for their comments on our recent article on using temperature trajectories to identify sepsis subphenotypes (1). Using group-based trajectory modeling, we identified four subphenotypes with different demographics, physiological characteristics, and levels of inflammatory markers, and we hypothesized an immunological basis for these subphenotypes. Supporting our hypothesis of a connection between temperature and immunological markers, Leijte and colleagues present a human endotoxemia model revealing correlation between temperature slopes and levels of endogenous pyrogens (IL-6 and TNFα [tumor necrosis factor α]) in healthy volunteers after administration of *Escherichia coli* endotoxin (2). This data provide evidence for the relationship between body temperature and cytokine responses. In addition, the data use dynamic temperature measurement (i.e., temperature slopes) to study associations with cytokine levels. This finding aligns with our work indicating that dynamic measures of temperature (i.e., temperature trajectory, variability, and slopes) may have more significance than static measures.

Although the cytokine responses in this study provide an immunological basis for our hypothesis, the systemic inflammatory response is intentionally self-limited in these healthy volunteers. We believe that measurement of cytokine levels in naturally occurring sepsis would add further information to the relationship between the thermoregulatory and immunological systems. Sepsis is defined as a dysregulated immunological response to infection. After the initial endotoxin-driven cytokine storm in sepsis, there is a protracted dysregulated immunological process that follows. We propose that temperature trajectories may elucidate not only the initial cytokine response but also the sustained immunological process in patients with sepsis. For instance, hyperthermic, slow resolvers may have sustained high levels of proinflammatory cytokines, whereas hyperthermic, fast resolvers may have the same initial proinflammatory cytokine storm followed by a defervescence process. We look forward to studies such as those of Dr. Leijte, Dr. Kox, and Dr. Pickkers to illuminate the relationship between temperature and the immunological system. ■

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Integrating Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Severe Acute Respiratory Distress Syndrome

To the Editor:

We read with great interest the study of Araos and colleagues (1), who elegantly demonstrated that near-apneic ventilation decreased lung injury and early fibroproliferation in an animal model of extracorporeal membrane oxygenation (ECMO)-supported acute respiratory distress syndrome (ARDS). Although minimizing risks of ventilator-induced lung injury on venovenous ECMO is paramount, the risks/benefits of strategies employed to minimize ventilator-induced lung injury also merit due consideration.

First, a demonstration that near-apneic ventilation with moderate positive end-expiratory pressure does not promote atelectasis and worsen intrapulmonary shunt fraction in that study may have been particularly helpful. Blood flow through the diseased pneumonic lung or lungs or parts of the lung that have collapsed will contribute to intrapulmonary shunting, also referred to as venous admixture. The shunt fraction is the calculated estimate of how much hypoxic blood should return to the arterial side after passing through the shunt to produce the measured arterial oxygen results, for a given $\dot{Q}$. The lung is a mixture of heterogeneous units, each with a different $\dot{V}/\dot{Q}$ ratio that can be severely affected by the loss of hypoxic vasoconstriction on venovenous ECMO. In addition, hypoventilation induced by extracorporeal carbon dioxide removal can lower the global $\dot{V}/\dot{Q}$ ratio of the native lungs and results in reabsorption atelectasis, therefore worsening hypoxemia (2). During near-apneic ventilation in severe ARDS, the contribution of native lungs to oxygenation is obviously significantly reduced. This makes the patient near-total ECMO dependent for oxygenation, often requiring high ECMO blood flows in the setting of a high $\dot{Q}$ state.

Second, as reported by the authors, the very low respiratory rate contributed significantly to the marked decrease in mechanical power observed in the near-apneic group. It should be noted that our understanding of the complex heart–lung–ventilator ECMO interactions are still evolving. Given that venovenous ECMO is a therapy delivered over weeks to months, the benefits of extreme lung protection should be balanced against risks associated with such strategies. We need to ensure that ventilation strategies employed on ECMO do not limit our ability to provide evidence-based supportive measures such as fluid restriction, minimization of sedation, and pharmacologic paralysis and early rehabilitation. To date, potential clinical benefits have only been demonstrated with a ventilation strategy that employed moderate positive end-expiratory pressure and limited plateau pressures $\leqslant$24 cm H_2O (3, 4). Last, moving forward, there is a sound physiologic rationale to reinforce the ventilator strategy employed in the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial with prone positioning. Although ECMO provides lung protection, prone positioning may further improve respiratory system compliance and $\dot{V}/\dot{Q}$ matching (5, 6). This may minimize reliance on higher ECMO blood flows with such extreme mechanical ventilation reduction strategies until the risk/benefit ratio of such strategies is clearly established. ■

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