Is *BMAL1* Just One Song Impacting the Circadian Dance of Lung Injury?

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To the Editor:

We read with interest the article by Felten and colleagues on ventilator-induced lung injury (VILI) in the *Journal* (1). We commend the authors on their work. We found it interesting to note that the authors evaluated *BMAL1* as it relates to VILI, whereas previous studies have evaluated *REV-ERBα* and other clock genes in asthma as well as VILI (2, 3). The authors demonstrated *BMAL1* deficiency in myeloid cells in mice, not in epithelial cells, which show differences in mechanical ventilation–induced immune cell recruitment, alveolar-capillary permeability, and oxygen impairment; yet, it is important to note that laboratory mice generally do not produce melatonin and are considered nocturnal animals, unlike diurnal humans. The authors attempt to mitigate this difference by evaluating mice at zeitgeber time (ZT0 vs. ZT12; regular light-dark [LD]) in some experiments while using the constant darkness (DD; before 24 h) in other experiments. The authors demonstrate a protective effect of VILI in *BMAL1* myeloid deficient knockout (KO) mice. We question the status of *REV-ERBα* and other core clock genes at the transcriptional and translational levels in the lungs of wild-type mice in the regular LD cycle versus DD and *BMAL1* LyzM-flox and *BMAL1* LyzM-KO mice CT0 versus CT12. Do the authors have any data to support the status of other core clock expression in myeloid cells that is different in *BMAL1* LysM-KO versus *BMAL1*-flox mice that may have contributed to the protective response observed in VILI? What is the possible explanation for the observed difference in circadian clock transgenic mouse models? We are intrigued with why *BMAL1* LyzM-KO mice show differences in susceptibility to lung injury as reported from other preclinical studies (4, 5). We find it interesting but uncertain why *BMAL1* myeloid cell–specific KO was the focus of this study of the multiple other known clock genes and circadian rhythm established in other lung tissue, including structural and immune cells.

It is well known that mechanical ventilation leads to release of inflammatory mediators, increasing alveolar wall injury, and contributing to development of VILI. The authors note during the study that the ventilatory settings increased to represent a "dynamic clinical outcome range" (high V_T, 1:1 – 34 ml/kg; inspiratory/expiratory ratio, 1:1). It would be beneficial for readers to understand the reasoning for using escalated settings of mechanical ventilation, because this would cause hemodynamic changes that could affect inflammatory marker release, possibly changing study results between different experimental ZT0/ZT12 (LD) compared with circadian time zero CT0/CT12 (DD). It is worth noting that 5 of 10 mice underwent premature termination because of hypotension during this portion of the study.

In addition, nutrient intake schedules impact circadian rhythm and were not addressed. Feeding, essential in animals, is regulated by homeostatic mechanisms and correlated temporally by the brain throughout the ∼24-hour circadian cycle. Metabolic hormones guide nutrient intake, and circadian disruption and mistiming can have deleterious effects on health (6). Treatment with mechanical ventilation and timing for the acquisition of nutrients during mechanical ventilation may be in direct opposition with each other. Moreover, circadian rhythm can impact pulmonary medication effectiveness (7). With this in mind, this work by Felten and colleagues demonstrates that lung inflammation may be impacted by circadian rhythms, which should guide further translational research on the molecular mechanism of circadian rhythms and the multiple clock genes as they relate to chronotherapy in the critically ill and across chronic pulmonary disease states. This research would provide a stronger impact if the argument for using *BMAL1* above other clock genes and the translational impact on this study's guidance of chronotherapy were clear. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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