14. Chakarov S, Lim HY, Tan L, Lim SY, See P, Lum J, *et al.* Two distinct interstitial macrophage populations coexist across tissues in specific subtissular niches. *Science* 2019;363:eaau0964.
15. Ogawa T, Shichino S, Ueha S, Bando K, Matsushima K. Profibrotic properties of C1q^{+} interstitial macrophages in silica-induced pulmonary fibrosis in mice. *Biochem Biophys Res Commun* 2022;599: 113–119.

Beating the Clock in Ventilator-induced Lung Injury

Circadian clocks organize behavior and physiology to an approximately 24-hour rhythm, facilitating adaptation to the environmental cycle of day and night. Mounting evidence links abnormal circadian alignment of behaviors like eating, sleeping, and light exposure to adverse health outcomes (1, 2). Critical illness, and possibly the intensive care environment itself, disrupts the endogenous circadian clock and may drive pathophysiological responses (3). For example, concentrations of melatonin, its precursors and metabolites, temperature, blood pressure, and the cellular transcriptome oscillate in grossly abnormal circadian patterns in critically ill patients (4, 5).

Autonomous molecular clocks present in every cell are synchronized *in vivo* by systemic signals, including autonomic innervation and hormone fluctuations that are coordinated by a master clock in the hypothalamic suprachiasmatic nuclei (6, 7). Clock-mediated differences in cellular function, created by oscillations in gene expression, might make the tissue more vulnerable to physiologic insult depending on the time of day. In the lung, inflammation is circadian, as has been noted in asthma and circadian variation in myeloid cell trafficking (8, 9). The relevant question for intensivists interested in translating physiologic insights into patient care is whether common intensive care interventions affect the body differently according to the time of day.

In this issue of the *Journal*, Felten and colleagues (pp. 1464–1474) tested the hypothesis that ventilator-induced lung injury (VILI) is a clock-dependent phenomenon. Investigators entrained mice in a 12 hour:12 hour light:dark cycle. Rodents are typically nocturnal mammals, as compared with diurnal humans, although strain-specific patterns are not always restricted to the dark (i.e., active phase). Once entrained, mice were subjected to varying degrees of injurious mechanical ventilation at either the beginning of the rest (dawn) or the active phase (dusk) of the circadian rhythm (10). They observed greater lung injury from exposures occurring during the rest phase of the circadian cycle. The differential harm was observed histologically in neutrophil recruitment, barrier permeability, inflammatory cytokine production, and hyaline membrane structure. Most importantly, there were measurable functional differences in lung compliance, inspiratory capacity, and lung permeability, resulting in more impaired oxygenation. Several steps were taken to sequentially confirm the pathogenesis of these time-dependent effects, including experiments in a clock gene (BMAL-1) knockout model, in which previously seen myeloid cell-specific diurnal variation in VILI was abated, making mice less susceptible to VILI-induced pathology (10).

The results of this study are both intriguing and exciting as they confirm that the degree of induced lung injury, and perhaps subsequent morbidity, is circadian-dependent. How might this influence intensive care? Chronotherapy, the intentional timing of treatments to maximize benefits and minimize adverse effects, has already become established in other fields. One of the most well-known applications is the timing of statin therapy, for which numerous studies have consistently demonstrated greater benefit with evening dosing (11). Tumorigenesis is also circadian, and chronochemotherapy has attracted substantial interest (12).

Embracing circadian supportive practices such as how we feed patients (e.g., daytime bolus feeding), care patterns (e.g., clustering of activities to daytime hours), and day–night cycle sensitive building design (e.g., natural light exposure) may have a significant impact on patient outcomes (13). Although the timing of some aspects of ICU care cannot be controlled (e.g., need to intubate or unplanned admission), others can be (e.g., when to complete a bronchoalveolar lavage or take a patient back to surgery). Studies such as the present work by Felton and colleagues are important because they identify candidate mechanisms that are clinically important and exhibit a rhythmic risk profile.

VILI is a major complication of intensive care, and some pathways that mediate VILI are affected by clock gene agonists such as REV-ERB agonists, for example, the NLRP3 inflammasome. Targeting REV-ERB may abate activation of the inflammasome, thereby mitigating VILI (14). In a rat model, the REV-ERB agonist SR9009 rescued many of the deleterious changes induced by high tidal ventilation (15). Although there are no longitudinal studies of circadian rhythm throughout an ICU stay, it is possible that encouraging cell clock renormalization can improve recovery. Given the importance of circadian-organized physiology, the future practice of critical care may eventually entail a bundle of clock-entraining interventions together with judicious timing of discrete invasive procedures and other care to optimize outcomes. ■

Originally Published in Press as DOI: 10.1164/rccm.202212-2268ED on January 11, 2023

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

M. Elizabeth Wilcox, M.D., Ph.D.
Interdepartmental Division of Critical Care Medicine
University of Toronto
Toronto, Ontario, Canada

Matthew B. Maas, M.D., M.S.
Department of Neurology
Northwestern University
Chicago, Illinois
and
Department of Anesthesiology
Northwestern University
Chicago, Illinois

References

1. Chellappa SL, Vujovic N, Williams JS, Scheer FAJL. Impact of circadian disruption on cardiovascular function and disease. *Trends Endocrinol Metab* 2019;30:767–779.
2. Gale JE, Cox HI, Qian J, Block GD, Colwell CS, Matveyenko AV. Disruption of circadian rhythms accelerates development of diabetes through pancreatic beta-cell loss and dysfunction. *J Biol Rhythms* 2011;26:423–433.
3. Telias I, Wilcox ME. Sleep and circadian rhythm in critical illness. *Crit Care* 2019;23:82.
4. Maas MB, Lizza BD, Abbott SM, Liotta EM, Gendy M, Eed J, *et al.* Factors disrupting melatonin secretion rhythms during critical illness. *Crit Care Med* 2020;48:854–861.
5. Maas MB, Iwanaszko M, Lizza BD, Reid KJ, Braun RI, Zee PC. Circadian gene expression rhythms during critical illness. *Crit Care Med* 2020;48: e1294–e1299.
6. Balsalobre A, Damiola F, Schibler U. A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell* 1998;93:929–937.
7. Schibler U, Gotic I, Saini C, Gos P, Curie T, Emmenegger Y, *et al.* Clock-talk: interactions between central and peripheral circadian oscillators in mammals. *Cold Spring Harb Symp Quant Biol* 2015;80: 223–232.
8. Durrington HJ, Farrow SN, Loudon AS, Ray DW. The circadian clock and asthma. *Thorax* 2014;69:90–92.
9. Druzd D, de Juan A, Scheiermann C. Circadian rhythms in leukocyte trafficking. *Semin Immunopathol* 2014;36:149–162.
10. Felten M, Ferencik S, Teixeira Alves L-G, Letsiou E, Lienau J, Müller-Redetzky HC, *et al.* Ventilator-induced lung injury is modulated by the circadian clock. *Am J Respir Crit Care Med* 2023;207: 1464–1474.
11. Maqsood MH, Messerli FH, Waters D, Skolnick AH, Maron DJ, Bangalore S. Timing of statin dose: a systematic review and meta-analysis of randomized clinical trials. *Eur J Prev Cardiol* 2022;29: e319–e322.
12. Sancar A, Van Gelder RN. Clocks, cancer, and chronochemotherapy. *Science* 2021;371:eabb0738.
13. Poole J, Ray D. The role of circadian clock genes in critical illness: the potential role of translational clock gene therapies for targeting inflammation, mitochondrial function, and muscle mass in intensive care. *J Biol Rhythms* 2022;37:385–402.
14. Liu H, Gu C, Liu M, Liu G, Wang D, Liu X, *et al.* Ventilator-induced lung injury is alleviated by inhibiting NLRP3 inflammasome activation. *Mol Immunol* 2019;111:1–10.
15. Li H, Wang C, Hu J, Tan J. A study on circadian rhythm disorder of rat lung tissue caused by mechanical ventilation induced lung injury. *Int Immunopharmacol* 2014;18:249–254.

Primary Spontaneous Pneumothorax: Treat the Patient, Not the X-Ray

In this issue of the *Journal*, Marx and colleagues (pp. 1475–1485) reported the largest randomized controlled trial on the management of primary spontaneous pneumothorax (PSP) (1). The Comparison of Exsufflation Versus Drainage in Primary Spontaneous Pneumothorax (EXPRED) trial randomized (at a 1:1 ratio) 402 patients from 31 emergency departments in France to undergo simple aspiration or insertion of a chest tube.

PSP predominantly affects young people with no significant underlying lung diseases. Its diagnosis and monitoring are always made on imaging, usually with chest X-rays (CXRs) (2). Throughout past decades, clinicians have focused first-line management of PSP on correcting the radiographic abnormality. Prompt and full reexpansion of the lung is considered the key priority. A variety of drainage techniques have been used to evacuate the pleural air. Large-bore chest tubes, often aided by suction and obsessive apical positioning of drainage tubes, have become the default practice in many centers to achieve the best radiographic lung expansion.

Originally Published in Press as DOI: 10.1164/rccm.202302-0273ED on March 9, 2023

However, large-bore chest tubes are known to cause pain, and their insertion also poses recognized risks. Less invasive alternative methods to evacuate air have been assessed. Aspiration of the air via different types of needles or small catheters is an attractive option and has been included in clinical guidelines (3, 4) as an alternative to chest tube drainage after several smaller randomized controlled trials showed promising results (5–7).

Although clinicians are willing to entertain less invasive options for "smaller" PSP, most still consider it "safer" to default to large-bore tube drainage if the CXR shows a sizeable pneumothorax. The EXPRED trial (1) specifically addresses the role of simple aspiration in patients with a complete pneumothorax, defined as radiographic separation of the lung, from its apex to the base, from the lateral chest wall. In the trial, simple aspiration was performed with a catheter connected to a suction device at -25 cm H_2O (to avoid variations associated with manual aspiration) for 30 minutes. A second bout of suction was allowed if needed. In the control group, patients underwent insertion of 16- or 20-F chest tubes for drainage.

The primary endpoint of the trial followed those of many prior studies and centered on expansion of the lung (1). "Failure" was defined by any residual pneumothorax $\geq$2 cm on radiographs 24 hours after the intervention. The study was set up as a noninferiority trial, but the predicted failure rate in the control group (based on literature data) differed significantly from the actual