References

1. Gaudry S, Quenot JP, Hertig A, Barbar SD, Hajage D, Ricard JD, *et al*. Timing of renal replacement therapy for severe acute kidney injury in critically ill patients. *Am J Respir Crit Care Med* 2019; 199:1066–1075.
2. Donnelly J, Budohoski KP, Smielewski P, Czosnyka M. Regulation of the cerebral circulation: bedside assessment and clinical implications. *Crit Care* 2016;20:129.
3. Roy CS, Sherrington CS. On the regulation of the blood-supply of the brain. *J Physiol* 1890;11:85–158.17.
4. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, *et al*.; AKIKI Study Group. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016;375:122–133.
5. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, *et al*.; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018;379:1431–1442.
6. Osgood M, Compton R, Carandang R, Hall W, Kershaw G, Muehlschlegel S. Rapid unexpected brain herniation in association with renal replacement therapy in acute brain injury: caution in the neurocritical care unit. *Neurocrit Care* 2015;22:176–183.
7. Patel N, Dalal P, Panesar M. Dialysis disequilibrium syndrome: a narrative review. *Semin Dial* 2008;21:493–498.

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Pathological Sleep and Wakefulness in the ICU and Weaning Failure: A Causal Relationship?

To the Editor:

The contribution of Dres and colleagues (1) addresses an important clinical question, as changes from normal sleep physiology during invasive mechanical ventilation, with and without analgosedation, are not entirely understood and there may be an interaction between sleep and successful weaning. Understanding the impact of sleep on weaning is important, and interventions to normalize sleep during mechanical ventilation might affect outcomes (2–4). The question remains as to whether patients with atypical sleep or pathological wakefulness are more likely to fail spontaneous breathing trials and, subsequently, weaning.

In a small ($n = 31$) and heterogeneous cohort of mechanically ventilated ICU patients, the authors observed that patients who passed a spontaneous breathing trial successfully and were subsequently extubated showed higher levels of wakefulness than patients who failed the spontaneous breathing trial and those who passed the trial but clinically were not deemed ready for extubation (1). This was expressed by a novel marker of wakefulness level or sleep depth measure (the odds ratio product [ORP]) during a 15-hour electroencephalographic recording before the spontaneous breathing trial. Patients who failed the spontaneous breathing trial were more likely to exhibit a poor interhemispheric correlation of sleep depth or level of wakefulness, as expressed by the intraclass correlation coefficient between ORP in the right- and left-brain hemispheres, than those who passed the spontaneous breathing trial (1).

The authors present important results; however, there remain some limitations to be pointed out and considerations for the design of future studies.

Causality between low ORP levels or interhemispheric ORP asynchrony and weaning failure cannot be established based on the study design and diverse bias. The effect of various analgosedation regimes on ORP in the general ICU population is unknown, and there were differences between the studied groups. The authors looked at ORP at a single time point in a small and heterogeneous group of mechanically ventilated patients and did not elaborate on changes of ORP over time, or over the length of the ICU stay, which differed between the groups. There was limited information regarding previous sleep deprivation or measurement thereof, raising concerns about the sequel of pathological sleep measures and rebound effects. Days with analgosedation and, eventually, critical-illness neuromyopathy may have affected the findings, although it is surprising that the successfully extubated patients had the longest ICU stays. Any information on previously diagnosed sleep-disordered breathing is missing.

It is problematic to compare the group of patients who passed the spontaneous breathing trial but were not deemed ready for extubation with the extubated group, or with the group that failed spontaneous breathing trials. Being considered ready for extubation depended on a subjective clinical decision, and information on the decision pathways used is not provided. Reasons for failure to wean should be stated. Furthermore, there was no consistent "dose–response" relationship in the ORP measurements across the three groups, which underlines the difficulty with the comparisons and the interpretation of the results.

In addition, the suggested underlying pathophysiology of changes in sleep and their clinical implications should be further discussed. Data regarding neurofunctional and neuroimaging outcomes are missing and should be addressed to understand how low levels of ORP, low interhemispheric ORP correlations, atypical sleep, and pathological wakefulness affect these elements before the effect of atypical sleep on such complex outcomes as weaning failure can be conclusively considered.

The next step would be to study neurofunctional and neuroimaging outcomes with regard to atypical sleep and different levels of ORP over time, and the effects of different analgosedation protocols on ORP. Furthermore, we need to develop a study design that elucidates the causal relationship between sleep disturbance and weaning failure, find ways to standardize clinical decision-making, and study the effect of interventions to normalize sleep on weaning outcomes. ■

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References

1. Dres M, Younes M, Rittayamai N, Kendzerska T, Telias I, Grieco DL, *et al*. Sleep and Pathological Wakefulness at the Time of Liberation from Mechanical Ventilation (SLEEWE): a prospective multicenter physiological study. *Am J Respir Crit Care Med* 2019;199:1106–1115.
2. Thille AW, Reynaud F, Marie D, Barrau S, Rousseau L, Rault C, *et al*. Impact of sleep alterations on weaning duration in mechanically ventilated patients: a prospective study. *Eur Respir J* 2018;51:1702465.
3. Thille AW, Coudroy R, Reynaud F, Marie D, Barrau S, Rousseau L, *et al*. Impact of sleep alterations on weaning duration of mechanically ventilated patients: how much is bad? *Eur Respir J* 2018;52:1800979.
4. Esquinas AM, Steier JS, Karim HMR. Impact of sleep alterations on weaning duration of mechanically ventilated patients: how much is bad? *Eur Respir J* 2018;52:1800925.

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Reply to Schwarz *et al.*

From the Authors:

We are very grateful to Schwarz and colleagues for reading our article (1) and their fruitful comments, which we wish to address below.

First, Schwarz and colleagues point out that any causal relationship between low odds ratio product (ORP) levels and weaning failure cannot be established from our data. They also highlight that the ORP level evaluation was made "at a single time point" and that potentially important information (previous sleep deprivation and previously diagnosed sleep disorders) was missing. Given the observational and exploratory nature of our study, we acknowledge that the design was not intended to reveal any causal relationship between the ORP findings and weaning outcomes. This study investigating ORP is the first to be conducted in an ICU setting, and further studies will have to determine whether the association between low ORP or interhemispheric ORP correlation and poor weaning outcome results from causality. Nevertheless, in a recent study, Thille and colleagues reported that patients with weaning failure were more likely to have pathological wakefulness (2). We actually observed an association between a low level of right-/left-brain hemisphere ORP correlation and reaching a normal ORP level (Figure 6 in our article). We therefore believe that there might be a possible link between a low level of ORP and poor weaning outcome. It is true that ORP—as reported in our study—reflects the average ORP in the whole study period, from 5 P.M. to 8 A.M. Consequently, we may have missed some relevant changes that occurred during the night. In a sensitivity analysis not shown in the article, we addressed this issue by assessing ORP over tertiles of the night and did not observe different findings. Of note, we had excluded patients with known sleep-disordered breathing.

Second, Schwarz and colleagues raise concerns about the weaning process and the process used in deciding to extubate. They also questioned the reasons for patients' failure to wean. However, Table E1 in the online supplement of our article provides the reasons for spontaneous breathing trial (SBT) failures and for not extubating patients who passed the SBT. Regarding the weaning process, all details are provided in the METHODS section of our article, but we totally agree that the evaluation of success (or failure) of the SBT remains subjective. However, as stated in METHODS, predefined criteria were used by the clinical team (3). Another important point is that the same SBT protocol was used for all of the patients (4). We believe that this approach may have reduced the subjective bias of the clinical evaluation. In addition, we also provide in the online supplement the results from an analysis of two groups: successful SBT and failed SBT. This analysis provided the same findings as the primary analysis.

Third, Schwarz and colleagues suggest some further areas of research that we think are highly relevant, including the effects of various analgosedation regimes. The assessment of ORP levels in combination with neuroimaging and neurofunctional data certainly deserves attention, and further studies are needed to consider this important objective. Schwarz and colleagues indicate some interesting leads in this regard. ■

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References

1. Dres M, Younes M, Rittayamai N, Kendzerska T, Telias I, Grieco DL, *et al*. Sleep and Pathological Wakefulness at the Time of Liberation from Mechanical Ventilation (SLEEWE): a prospective multicenter physiological study. *Am J Respir Crit Care Med* 2019;199:1106–1115.

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