Clarifying the Effect of Sleep Deprivation on the Respiratory Muscles

In this issue of the *Journal*, Rault and colleagues (pp. 976–983) assessed the effect of one night of sleep deprivation on respiratory motor output and inspiratory endurance in 20 healthy men (1). Inspiratory endurance was decreased by 50%, and preinspiratory motor potentials, thought to reflect activity of the supplementary motor area, were decreased by 40%. Dyspnea developed more rapidly after sleep deprivation. The investigators conclude that one night of sleep deprivation decreases cortical contribution to respiratory motor output, with a consequent decrement in inspiratory endurance.

Rault and colleagues (1) present convincing arguments for a mechanistic link between (partial) inhibition of the supplementary motor area and decreased inspiratory endurance. Their findings raise several questions: Why is dyspnea worse after sleep deprivation? What is the effect of sleep deprivation on the primary motor cortex and spinal and supraspinal reflexes during submaximal inspiratory loading? What are the clinical implications?

To quantify dyspnea, the investigators instructed participants to report discomfort associated with breathing: the affective dimension of dyspnea, analogous to the unpleasantness of pain (2). During laboratory-generated dyspnea neuroimaging, studies have revealed activation of several corticolimbic structures, including the amygdala, right anterior insula, cingulate gyrus, and medial thalamus (3). Sleep deprivation increases cerebral blood flow in many of these corticolimbic structures (4). This raises the possibility that a component of decreased inspiratory endurance associated with sleep deprivation was related to increased perception of dyspnea, a possibility raised by the investigators themselves.

Breathing discomfort and the sensory quality of dyspnea can prompt powerful emotional responses (fear, anxiety) (2). Sleep deprivation enhances emotional reactivity (5). Rault and colleagues (1) did not assess the emotional response to inspiratory loading (2), nor did they record the sensory dimensions of dyspnea, such as air hunger and breathing effort (2). Two observations suggest these sensory dimensions were unlikely players in the reduction of endurance. Sleep deprivation had no effect of end-tidal carbon dioxide. Sleep deprivation was associated with an 11.1% decrease in V_T and a 25.9% decrease in the electrical activity of the diaphragm, suggesting no increase in corollary discharges (3).

At the limit of submaximal inspiratory loading (task failure), breathing discomfort was near maximal both after normal sleep and after sleep deprivation. At task failure, diaphragmatic recruitment was 40% of maximum after normal sleep and 20% of maximum after sleep deprivation. Submaximal diaphragmatic recruitment in the presence of unsustainable dyspnea suggests reflex inhibition of central neural output (central fatigue) (6), a consideration brought up by the investigators themselves. This reflex inhibition, if present, was more intense after sleep deprivation. These findings raise the possibility that sleep deprivation can enhance the spinal and supraspinal mechanisms responsible for central fatigue at the limit of submaximal inspiratory loading.

Rault and colleagues (1) reason that the primary motor cortex had no role in reducing endurance time. Supporting this likelihood, they note that participants were always able to maximally recruit the diaphragm. The association between explosive maximal voluntary contractions and sustained (submaximal) efforts is not straightforward. As the investigators note, continuous submaximal loading (such as during endurance testing) activates fewer phrenic motoneurons and fewer brain areas than single loading activities (7). To better characterize the effect of sleep deprivation on the primary motor cortex, Rault and colleagues (1) could have recorded motor evoked potentials elicited by single and paired transcranial magnetic stimulation. With this technique, some investigators have reported an association between sleep deprivation and decreased corticospinal excitability (8), decreased intracortical inhibition (9, 10), and either a decrease (9) or an increase (8) in intracortical facilitation. (Intracortical inhibition and facilitation are thought to reflect excitability of separate populations of interneurons intrinsic to Brodmann cortical area 4 [9].)

Cortical responses to transcranial stimulation raise several considerations. It is likely that the primary motor cortex in the subjects of Rault and colleagues (1) was affected by sleep deprivation. This effect might have contributed to the decrement in endurance by decreasing corticospinal excitability (8) and intracortical facilitation (9), or it might have curbed the endurance decrement by lessening intracortical inhibition (9, 10) and enhancing intracortical facilitation (8). The last two phenomena have been described mainly (9), if not exclusively (8, 10), in women. Rault and colleagues (1) circumvented this concern by only enrolling men. It would be incorrect to extrapolate the results to women.

Does the model of sleep deprivation of Rault and colleagues (1) shed light on the link between abnormal sleep and respiratory failure (11, 12)? Yes. Ventilated patients experience low sleep efficiency and electroencephalographic shift to slow frequencies and loss of spindle formation (11, 12), findings consistent with sleep loss (13). Conversely, the differences between a failed weaning trial and the endurance test used by Rault and colleagues (1) may limit generalizability. The mechanical load during a failed weaning trial progressively increases (14), whereas mechanical load during endurance testing was constant (1). During a failed trial (15), patients maintain steady tidal swings of electrical activity of the diaphragm throughout the trial. With sleep deprivation, volunteers experienced a progressive decrease in tidal

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electrical activity of the diaphragm (1). Whether (central) inhibition (or inhibition of the supplementary motor cortex) is present in ventilated patients with abnormal sleep remains to be determined.

The elegant investigation of Rault and colleagues (1) is provocative. The investigators have set the stage for the objective study of the physiologic maze that accompanies sleep deprivation. One challenge will be to unravel the sex-specific effect of sleep deprivation on dyspnea, spinal and supraspinal reflex inhibition, and function of the primary motor cortex. Another challenge will be to determine the effect of sleep deprivation in critically ill patients, including those who fail invasive and noninvasive ventilation. The challenge is formidable, but now is the time to tackle it. ■

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Latent Tuberculosis Infection–associated Immunodiagnostic Test Responses as Biomarkers of Incipient Tuberculosis: Fruitful or Futile?

Latent tuberculosis infection (LTBI) constitutes part of the TB disease spectrum (1, 2). The diagnosis and treatment of LTBI is important, as global eradication targets will not be attainable without treating LTBI (3).These considerations also apply to drug-resistant TB, which threatens to derail control efforts (4). The World Health Organization has recently recommended that close contacts of index cases of TB, even in TB endemic countries, should be considered for LTBI treatment (even if they are HIV-uninfected or not children) (5). However, the diagnosis of LTBI is challenging. Unlike with active TB, in humans there is no microbiological or histopathological reference standard for LTBI, and one can only infer the potential presence of LTBI using immunodiagnostic tests, which enumerate the magnitude of

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