cumulative pathologies of the lung, pleura, diaphragm, chest wall, and abdomen. The MIP is effort-dependent, and it represents the combined power generated by the inspiratory muscles, including diaphragmatic contraction. Therefore, MIP measurement as a tool to assess and follow diaphragmatic contractility is limited (5). The diaphragmatic muscle weakness could be best assessed by the regional (subdiaphragmatic) change in inspiratory pleural pressure. Moreover, twitch transdiaphragmatic pressure (difference in gastric and esophageal pressures) in response to electrical or magnetic phrenic nerve stimulation can best assess the extent of diaphragmatic dysfunction.

Half of the patients were tracheostomized, and liberation from mechanical ventilation in these patients could be less challenging than in those who were intubated (6). And weaning from ventilation in patients who are endotracheally intubated involves both liberation from ventilation and successful extubation. Moreover, respiratory load and work of breathing have been reported to be lower in patients who are tracheostomized than endotracheally intubated. The clinical predictors and severity of pathologies are generally different between patients who are tracheostomized and endotracheally intubated. Therefore, these two clinical phenotypes require a separate analysis to assess the effect of phrenic nerve stimulation. In conclusion, considerable heterogeneity in the study population seemed to influence the finding and interpretation of this study. ■

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Reply to Jha

From the Authors:

We thank Dr. Jha for his reading of our study (1) and for his valuable and insightful comments. We wish to address some of the comments made by Dr. Jha.

First, Dr. Jha points out that our exclusion criteria did not mention risk factors for failure of liberation from mechanical ventilation. However, we would like to stress that patients with overt congestive heart failure at the time of liberation from mechanical ventilation could not be enrolled until clinicians estimated that another reason might explain weaning failure. In our study, we purposely did not select patients on the basis of the presence of diaphragm function, for two reasons: first, it has been established that diaphragm dysfunction is present in a majority of patients at the time of liberation from mechanical ventilation (2), and second, liberation from ventilation depends on the balance of respiratory muscle load and capacity, and any improvement in diaphragm function is likely to facilitate safe extubation despite the lack of severe diaphragm dysfunction. Dr. Jha mentions that "differential distribution of lung collapse, atelectasis, lung fibrosis, diastolic dysfunction and pulmonary hypertension in the control and treatment arm could have affected the outcomes." In addition, Dr. Jha notes that in our study, there were several risk factors for diastolic dysfunction. We completely agree with this comment, and we believe that the randomization process was the best way to allocate equal proportions of patients with lung and cardiac diseases to the treatment and control groups. We also agree with Dr. Jha that lung ultrasound–based aeration score and echocardiography are interesting tools in this context, as reported in a recent study from our group (3). However, in our multicenter study, it was not deemed feasible to ask investigators to perform echocardiography and lung ultrasound. Regarding the assessment of regional variation in aeration by electrical impedance tomography, only a few centers in the world possess this technology.

Second, Dr. Jha underlines that "patients with overt congestive heart failure were to be excluded, however, the authors reported congestive heart failure in 9% of patients and valvular heart disease in 19% of patients in the treatment arm." We would like to clarify that only patients with overt congestive heart failure at the time of eligibility screening were not enrolled, but if clinicians could deal with fluid overload, patients were reassessed and eventually included despite the presence of chronic heart disease. We do not see any reason that would have required the exclusion of patients with chronic heart disease from our study. Indeed, we believe that the opposite would have been unethical.

Third, we appreciate the Dr. Jha's physiological description of maximum inspiratory pressure. We share his interpretation regarding the recruitment of extradiaphragmatic inspiratory muscles in the generation of maximal inspiratory pressure. As reported in several

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publications from our group (4–6), Dr. Jha is absolutely correct in saying that twitch transdiaphragmatic pressure is the reference method to specifically assess diaphragm function. Nonetheless, Dr. Jha should fairly recognize that measuring diaphragm function according to twitch pressure is simply not possible at the scale of an international multicenter trial. Following Dr. Jha's reasoning, the fact that there was a significant increase in maximal inspiratory pressure in the treatment group and not in the control group works in favor of the treatment.

Last, Dr. Jha rightly points out the heterogeneity of our population, in particular the fact that half of the patients were tracheostomized. As suggested by Dr. Jha, we provide here a sensitivity analysis pertaining to the tracheostomized patients. Fifty-two patients were tracheotomized at study entry. Among them, weaning was successful in 79.8% in the treatment group and 72.4% in the control group. Forty-six patients had endotracheal tubes. Among them, weaning was successful in 82.1% in the treatment group and 76.0% in the control group. Further studies will be required to confirm these findings. ■

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Carbonic Anhydrase Inhibitors: A New Dawn for the Treatment of Obstructive Sleep Apnea

To the Editor:

With interest, we read the paper of Hedner and colleagues (1), which confirms that sulthiame (a carbonic anhydrase inhibitor [CAI]) showed a satisfactory safety profile in moderate and/or severe obstructive sleep apnea (OSA) and reduced OSA, on average, by more than 20 events/h, one of the strongest reductions reported in a drug trial in OSA. OSA causes a series of brief, severe episodes of hypoxia and hypercapnia, resulting in persistent, maladaptive chemoreflex-mediated activation of the sympathetic nervous system. Although passive critical closing pressure of the upper airway-anatomy is an important determinant, abnormalities in nonanatomic traits are also present in most patients with OSA (2). An important factor in OSA is high circulatory gain, which is not only a driver of central sleep apnea but also a major contributor to the pathogenesis of OSA in 30–40% of patients (3). Individuals with high loop gain tend to experience periodic declines in respiratory drive, resulting in decreased activation of the upper airway dilator muscles, leading directly to repetitive breathing events (i.e., OSA), an important ventilatory regulator of which is carbonic anhydrase, which is also the rationale for CAIs in the treatment of individuals with OSA (4, 5). The results of this study and previous studies (6, 7) provide a solid

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