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. ■

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

Martin Dres, M.D., Ph.D.*
Experimental and Clinical Respiratory Neurophysiology
Sorbonne University, INSERM
Paris, France

and

Medicine Intensive Reanimation (R3S Department)
AP-HP, Pitie-Salpetriere Hospital
Paris, France

Marcelo Gama de Abreu, M.D.
Department of Anesthesiology and Intensive Care Medicine
Technische Universitat Dresden
Dresden, Germany

Department of Intensive Care and Resuscitation
and
Department of Outcomes Research
Cleveland Clinic
Cleveland, Ohio

Thomas Similowski, M.D.
Experimental and Clinical Respiratory Neurophysiology
Sorbonne University, INSERM
Paris, France

and

Medicine Intensive Reanimation (R3S Department)
AP-HP, Pitie-Salpetriere Hospital
Paris, France

On behalf of the RESCUE-2 Investigators

ORCID IDs: 0000-0001-9191-6089 (M.D.); 0000-0003-2868-9279 (T.S.).

*Corresponding author (e-mail: martin.dres@aphp.fr).

References

1. Dres M, de Abreu MG, Merdji H, Müller-Redetzky H, Dellweg D, Randerath WJ, *et al.*; RESCUE-2 Study Group Investigators. Randomized clinical study of temporary transvenous phrenic nerve stimulation in difficult-to-wean patients. *Am J Respir Crit Care Med* 2022;205:1169–1178.
2. Dres M, Goligher EC, Heunks LMA, Brochard LJ. Critical illness-associated diaphragm weakness. *Intensive Care Med* 2017;43:1441–1452.
3. Dres M, Rozenberg E, Morawiec E, Mayaux J, Delemazure J, Similowski T, *et al.* Diaphragm dysfunction, lung aeration loss and weaning-induced pulmonary oedema in difficult-to-wean patients. *Ann Intensive Care* 2021;11:99.
4. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. *N Engl J Med* 1991;325:917–923.
5. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, *et al.* Diaphragm dysfunction on admission to the intensive care unit: prevalence, risk factors, and prognostic impact-a prospective study. *Am J Respir Crit Care Med* 2013;188:213–219.
6. Dres M, Dubé B-P, Mayaux J, Delemazure J, Reuter D, Brochard L, *et al.* Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. *Am J Respir Crit Care Med* 2017;195:57–66.

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

Supported by Natural Science Foundation of Guangdong Province grant (2021A1515011373 and 2019A1515010981).

Author Contributions: R.C., H.L., X.C., C.W., Z.Z. and H.W. wrote the initial draft of the manuscript. J. Lu, Junyan Lin, Z.H., Jiangpeng Lin, N. Zhong, and N. Zhang contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202206-1209LE on July 12, 2022

theoretical basis for exploring long-term treatment with CAIs for OSA and determining the most effective dose, with cross-generational significance.

In Hedner and colleagues' study (1), 4 weeks of sulthiame treatment had therapeutic effects (on apnea–hypopnea index [AHI] and sleep quality) on all patients with OSA, but at this time point, AHI has not yet decreased to the normal range. We believe the reasons why sulthiame treatment of OSA could not reduce AHI to normal may include the following: the time period of 4 weeks was too short, the selected patients were too ill, and the patient phenotype may not have been high loop gain. To address these influencing factors, we can begin with the following approaches: increase the treatment observation time and include patients with high loop gain and mild OSA. If CAIs have a better treatment effect on these phenotypes in patients with OSA, then the precise treatment of these patients will be more readily undertaken. We believe that suitable populations for sulthiame treatment for OSA include mainly individuals with high loop gain type, patients with mild OSA, patients with moderate to severe OSA who cannot tolerate continuous positive airway pressure therapy, patients with OSA who are not suitable for pharyngeal surgery, and individuals with postoperative residual OSA. Thereafter, we can continue to explore whether it is better to use CAIs combined with mandibular advancement devices or combined with tongue and facial muscles.

In view of the foregoing considerations, although the sample size of Hedner and colleagues' study (1) was small, the study shows that CAIs can be used as a new drug treatment to reduce disease severity and complications among patients with OSA. A long-term, multicenter study, with a large sample size, of the efficacy of CAI treatment is expected. In future studies, patients who are suitable for sulthiame treatment may be screened for precise treatment, which may have better therapeutic effects. ■

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

Acknowledgment: The authors thank Professor Nanshan Zhong of the State Key Laboratory of Respiratory Disease for constructive advice.

Riken Chen, M.D.*
Huizhao Liao, M.D.*
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou, Guangdong, China

State Key Laboratory of Respiratory Disease
Guangzhou, Guangdong, China

National Clinical Research Center for Respiratory Disease
Guangzhou, Guangdong, China

Guangzhou Institute of Respiratory Disease
Guangzhou, Guangdong, China

National Clinical Research Center for Respiratory Disease
Guangzhou, Guangdong, China

and

National Center for Respiratory Medicine
Guangzhou, Guangdong, China

Xiaojuan Chen, M.D.*
Medical College of Jiaying University
Meizhou, China

Chaoyu Wang, M.D.*
Taishan Hospital of Traditional Chinese Medicine
Jiangmen, China

Huiyu Wu, M.D.*
Guangzhou Institute of Technology
Guangzhou China

Zhenzhen Zheng, M.D.*
The Second Affiliated Hospital of Guangdong Medical University
Zhanjiang, China

Jianmin Lu, M.D.
Junyan Lin, M.D.
Zijie Huang, M.D.
Jiangpeng Lin, M.D.
Nanshan Zhong, M.D.
Nuofu Zhang, M.D.‡
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou, Guangdong, China

State Key Laboratory of Respiratory Disease
Guangzhou, Guangdong, China

National Clinical Research Center for Respiratory Disease
Guangzhou, Guangdong, China

Guangzhou Institute of Respiratory Disease
Guangzhou, Guangdong, China

National Clinical Research Center for Respiratory Disease
Guangzhou, Guangdong, China

and

National Center for Respiratory Medicine
Guangzhou, Guangdong, China

ORCID ID: 0000-0001-6101-7891 (R.C.).

*These authors contributed equally to this work.
‡Corresponding author (e-mail: nfzhanggird@163.com).

References

1. Hedner J, Stenlöf K, Zou D, Hoff E, Hansen C, Kuhn K, *et al.* A randomized controlled clinical trial exploring safety and tolerability of sulthiame in sleep apnea. *Am J Respir Crit Care Med* 2022;205:1461–1469.
2. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea: identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188:996–1004.
3. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7: 687–698.
4. Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;163:1181–1190.
5. Wellman A, Jordan AS, Malhotra A, Fogel RB, Katz ES, Schory K, *et al.* Ventilatory control and airway anatomy in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;170:1225–1232.
6. Schmickl CN, Landry SA, Orr JE, Chin K, Murase K, Verbraecken J, *et al.* Acetazolamide for OSA and central sleep apnea: a comprehensive systematic review and meta-analysis. *Chest* 2020;158:2632–2645.
7. Eskandari D, Zou D, Grote L, Hoff E, Hedner J. Acetazolamide reduces blood pressure and sleep-disordered breathing in patients with hypertension and obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med* 2018;14:309–317.