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

Rebecca M. Baron, M.D.*
Brigham and Women's Hospital
Boston, Massachusetts

John W. Christman, M.D.
Ohio State University
Columbus, Ohio

Kathleen D. Liu, M.D., Ph.D.‡
Michael A. Matthay, M.D.
University of California, San Francisco
San Francisco, California

Wesley H. Self, M.D., M.P.H.
Vanderbilt University Medical Center
Nashville, Tennessee

Bryan J. McVerry, M.D.
University of Pittsburgh School of Medicine and University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Robert Duncan Hite, M.D.
University of Cincinnati College of Medicine
Cincinnati, Ohio

Robert Paine III, M.D.
University of Utah
Salt Lake City, Utah

Mark M. Wurfel, M.D., Ph.D.
University of Washington
Seattle, Washington

Nathan I. Shapiro, M.D., M.P.H.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Peter W. Adams, B.S., C.C.R.C.
University of Pittsburgh School of Medicine and University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Eric P. Schmidt, M.D., Ph.D.
University of Colorado Denver
Aurora, Colorado
and
Denver Health Medical Center
Denver, Colorado

Nancy Ringwood, R.N.
Massachusetts General Hospital
Boston, Massachusetts

and the Pathogenesis Committee of the NHLBI PETAL Network

*Corresponding author (e-mail: rbaron@partners.org).
‡K.D.L. is Associate Editor of *AJRCCM*. Her participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

References

1. CMRC IRB maximum allowable total blood draw volumes (clinical + research) [accessed 2020 Jun 19]. Available from: https://cdn.ymaws.com/www.safeta.org/resource/resmgr/kids/docs/blood_draws_maximum_allowabl.pdf.
2. US Department of Health and Human Services. OHRP expedited review categories. 1998 [accessed 2020 Jun 19]. Available from: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html.
3. Dana-Farber/Harvard Cancer Center. Guidance on maximum blood draw for research purposes [accessed 2020 Jun 19]. Available from: https://www.dfhcc.harvard.edu/crs-resources/ODQ_Documents/09_Investigator_Resources/Guidance_on_Maximum_Blood_Draw_for_Research_Purposes.pdf.
4. North Shore Long Island Jewish. Human subject protection program guidance document [accessed 2020 Jun 19]. Available from: https://feinstein.northwell.edu/sites/northwell.edu/files/2019-07/Maximum-Blood-Draw-Limits.pdf.
5. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, *et al*.; ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288: 1499–1507.
6. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, *et al*. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* 2019;321: 2003–2017.

Mild to Moderate Sleep Apnea Is Linked to Hypoxia-induced Motor Recovery after Spinal Cord Injury

To the Editor:

Acute intermittent hypoxia (AIH) is a novel treatment to enhance respiratory and nonrespiratory motor function after chronic incomplete spinal cord injury (SCI) (1–3). Despite promising findings, uncertainties in optimal AIH delivery to a heterogeneous population of persons with SCI remain a challenge to clinical translation. Beneficial AIH responses are variable between individuals, and we lack useful biomarkers to determine which individuals benefit most from treatment. AIH-induced functional benefits rely on mechanisms of AIH-induced neuroplasticity. Multiple factors modify AIH-induced plasticity in rodent models, including intermittent hypoxia preconditioning and systemic inflammation, among others (4, 5). One factor not accounted for in human AIH trials, to date, is the incidence of sleep-disordered breathing (SDB). Many individuals with SCI exhibit mild to moderate SDB (6), leading to extended periods of nocturnal high-dose intermittent hypoxia. Because chronic intermittent hypoxia (CIH) elicits both neuroplasticity and inflammation (5), SDB after SCI may contribute to between-person variations in response to AIH therapy.

Supported by the U.S. Department of Defense Spinal Cord Injury Research Program grant W81XWH-15-2-0045 and the NIH National Institute of Child Health and Human Development grant R01HD081274.

Originally Published in Press as DOI: 10.1164/rccm.202002-0245LE on May 5, 2020

Table 1. Patient Characteristics, Sleep Parameters, and Functional Gain after AIH Therapy (Cohen's *d*)

	No Apnea (*n* = 10)	Mild to Moderate Apnea (*n* = 10)	*P* Value*	Mild Apnea 5 ⩽ AHI < 15 (*n* = 7)	Moderate Apnea 15 < AHI < 30 (*n* = 3)
AHI, no./h†	1.5 (0–4)	9.0 (6–29)	<0.001	6.5 (6–10)	23 (17–29)
Cohen's *d*	0.2 ± 4.0	4.2 ± 3.8	0.043	2.4 ± 2.3	7.8 ± 4.6
Age, yr	46 ± 14	45 ± 8	0.90	42 ± 15	53 ± 14
Level of injury†	C5 (C2–T4)	C5 (C4–T8)	0.26	C5 (C5–T8)	C5 (C4–T3)
Time since injury, yr†	7 (3–38)	7 (3–25)	0.64	7.5 (6–18)	11 (7–24)
BMI, kg/m^2†	20 (19–30)	24 (20–33)	0.23	24 (20–25)	28 (24–33)
Sleep parameters					
Evaluation duration, h/night	6 ± 2	7 ± 2	0.42	6 ± 2	8 ± 1
Apnea index, no./h†	0 (0–2.5)	2.5 (0.5–27)	0.001	1.5 (0.5–4.3)	14 (0.5–27)
Hypopnea index, no./h	1.1 ± 0.9	5.6 ± 2.1	<0.001	5.1 ± 1.0	5.6 ± 3.7
Oxygen desaturation index, no./h†	1 (0–6)	10 (4–34)	<0.001	8.5 (4–13)	23 (4–34)
Average Sp_{O_2}, %	93 ± 4	91 ± 4	0.048	93 ± 2	89 ± 7
Average Sp_{O_2} nadir, %	91 ± 5	84 ± 6	0.005	87 ± 2	76 ± 3
Time with Sp_{O_2} ⩽ 90%, min†	2 (0–36)	67 (1–137)	0.002	48 (1–110)	85 (1–137)
Average pulse frequency, beats/min	65 ± 9	65 ± 10	0.95	65 ± 12	65 ± 6
Highest pulse frequency, beats/min	130 ± 41	114 ± 32	0.77	102 ± 29	140 ± 42
Snoring events, no./h	578 ± 673	653 ± 760	0.47	353 ± 411	1,353 ± 1,023

Definition of abbreviations: AHI = apnea–hypopnea index; AIH = acute intermittent hypoxia; BMI = body mass index; Sp_{O_2} = pulse oxygen saturation.
Data are mean ± SD except where otherwise noted.
*Comparison between "no apnea" and "apnea" (mild to moderate apnea) (*t* test or Mann-Whitney rank test comparisons).
†Median (range) for nonparametric variables.

Here, we report associations between SDB and AIH-induced motor recovery in individuals with chronic incomplete SCI. Specifically, we conducted a blinded continuing analysis in 20 participants who performed baseline sleep assessments and one of three clinical trials with similar experimental designs (1–3), including treatment methods, randomization (AIH/sham treatment), blindness, and washout period. Participants who missed an evaluation session ($n = 5$), were enrolled in more than

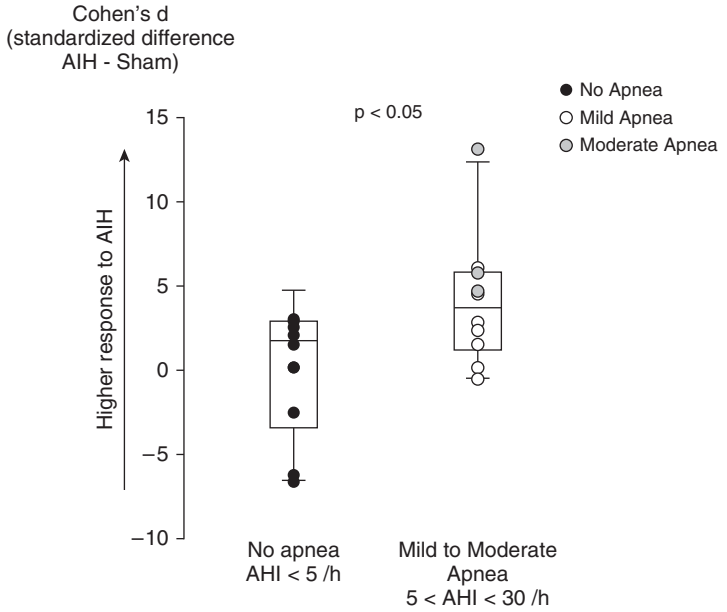

Figure 1. Effect of sleep-disordered breathing (as assessed by the apnea–hypopnea index [AHI]) on the response to acute intermittent hypoxia (AIH) therapy. Shown are individual values and box plot (median, 10th, 25th, 75th, and 90th percentiles with error bar) of Cohen's *d* in individuals with incomplete spinal cord injury and sleep apnea (mild to moderate apnea 5 < AHI < 30/h) or no apnea (AHI < 5/h).

one of these studies ($n = 5$) (in which case, we evaluated only the first study completed), or had <4 hours of sleep data duration ($n = 8$) were not included. Participants performed five consecutive (daily) AIH breathing treatment sessions (or a single-day session; $n = 3$). A manually controlled air delivery system (Hypoxico, Inc.) was used with 15 sequences of 60–90 seconds of low-oxygen breathing (AIH; $F_{I_{O_2}} = 0.10 \pm 0.02$) or room air (sham; $F_{I_{O_2}} = 0.21 \pm 0.02$) alternated with 60-second intervals of breathing room air. We compiled the apnea–hypopnea index, lowest O_2 pulse saturation (average pulse oxygen saturation [Sp_{O_2}] nadir), inspiratory flow limitations, snoring counts, and pulse frequency (ApneaLink; Resmed Corp.) and quantified associations between these metrics and AIH-induced improvements in motor function. We computed effect sizes to standardize analyses across trials with different functional outcome measures (limb strength, walking ability, or hand function). Within-subject Cohen's d scores corresponded with a participant's effect size after treatment and were calculated as follows: Cohen's d = [average change from baseline with AIH] − [average changes from baseline with sham]/baseline pooled SD (7).

Mild to moderate sleep apnea (5 < apnea–hypopnea index <30/h) occurred in 50% of study participants. The participants with mild to moderate apnea ($n = 10$) had the same characteristics as those without apnea ($n = 10$, Table 1). Participants with mild to moderate SDB demonstrated greater motor gains with AIH therapy (Cohen's d median: 3.6; range: −0.5 to 13.6) versus those without apnea (1.7; range: −6.6 to 4.9; $P = 0.043$) (Figure 1). Cohen's d positively correlated with the oxygen desaturation index (ODI-4%) ($r = 0.74$; $P < 0.0001$) and negatively correlated with the average Sp_{O_2} nadir ($r = -0.69$; $P = 0.001$). Moreover, the time spent during sleep with Sp_{O_2} below 90% also correlated to Cohen's d ($r = 0.51$; $P = 0.024$); in a multiple regression analysis ($r = 0.73$; $P = 0.002$), ODI-4% was an independent predictor of Cohen's d ($P = 0.007$), whereas time spent during sleep with Sp_{O_2} below 90% was not ($P = 0.56$), suggesting that the AIH response mostly related to repetitive nocturnal O_2 desaturations. Conversely, pulse frequency (sympathetic activity) or snoring events were not related to AIH response. Finally, Cohen's d did not correlate with Sp_{O_2} during AIH therapy (first and fifth sessions) ($r < 0.30$; $P > 0.25$).

Our results demonstrated that mild to moderate SDB is associated with more significant AIH-induced therapeutic benefits in people with chronic incomplete SCI. SDB (and associated CIH) may precondition AIH therapy, enabling larger responses to subsequent AIH treatments as reflected in improved AIH-induced performance gains. The dose–response between nocturnal O_2 desaturation and AIH-induced motor gains supports the hypothesis that a minimum hypoxia severity is necessary to induce motor adaptations (4). Based on available literature in rodent models, this effect may arise via CIH-preconditioning effects on carotid body chemoreceptors, enabling long-term sensory facilitation in carotid sinus nerve activity and amplification of chemoafferent integration within the central nervous system (8). However, given the lack of correlation between Sp_{O_2} during AIH therapy (an inverse indicator of respiratory chemoreflex) and AIH-induced motor gains, it seems unlikely that chemosensory plasticity would explain our results. Alternatively, spinal mechanisms may enhance the capacity for AIH-induced motor plasticity (4). For example, repetitive serotonin receptor activation may increase BDNF (brain-derived neurotrophic factor) protein synthesis and BDNF/TrkB (tropomyosin receptor kinase B) signaling, causing the functional synaptic plasticity that underlies beneficial effects of therapeutic AIH (9). In humans, reminder doses of three times/week maintain increases in walking speed and endurance for up to 5 weeks after 1 week of daily AIH (10). The independent effect of the repetitive occurrence of sleep apnea (ODI) on functional gain would support this hypothesis. Hence, plasticity in somatic motor output could result from cumulative repeated CIH/AIH.

Our results also suggest that SDB may serve as a "biomarker" that indicates the persons most likely to benefit from AIH therapy. It would be interesting to know if SDB itself (via mild to moderate CIH) is directly associated with better functional outcomes during normal rehabilitative therapeutics. However, because severity of hypoxia (dosage) and repetitive intermittent hypoxia are key components of metaplasticity, mild to moderate amounts of CIH may more likely precondition AIH therapy (4).

Participants accepted into this study did not have severe SDB; more severe SDB may lead to deleterious proinflammatory responses that inhibit AIH therapy–induced gains (5). Given the potential benefits of mild or modest CIH versus the known pathological impact of obstructive and central SDB on health, this study does not guide whether individuals with SCI need SDB treatment. Understanding the history of hypoxic exposures merits further consideration when evaluating therapeutic AIH dosing and efficiency.

Overall, our study demonstrates that AIH therapy–induced functional gains are more robust in people with chronic incomplete SCI and mild to moderate SDB. Repetitive nocturnal desaturation may precondition spared neural circuitry involved in functional tasks, enabling them to respond to subsequent AIH therapy more positively. If confirmed, these findings strongly suggest a need to refine AIH delivery protocols and that assessment of SDB provides valuable insight into individual responsiveness to AIH therapy. Further larger and dedicated studies are needed to confirm our findings and pursue the mechanisms by which mild to moderate SDB may precondition AIH therapy and favor motor recovery in SCI. ■

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

Acknowledgment: The authors thank the physical therapists and physicians who supported functional tests and therapies at Emory University's Department of Rehabilitation Medicine in Atlanta, GA, the Shepherd Center in Atlanta, GA, and the Shirley Ryan Ability Lab in Chicago, IL. The authors thank all study participants.

Isabelle Vivodtzev, Ph.D.*
Harvard Medical School
Boston, Massachusetts
Spaulding Rehabilitation Hospital
Boston, Massachusetts
Sorbonne Université
Paris, France
and
Inserm
Paris, France

Andrew Q. Tan, Ph.D.
Harvard Medical School
Boston, Massachusetts
and
Spaulding Rehabilitation Hospital
Boston, Massachusetts

Megan Hermann, P.T., D.P.T.
Arun Jayaraman, P.T., Ph.D.
Shirley Ryan AbilityLab
Chicago, Illinois

Victoria Stahl, Ph.D.
Emory University School of Medicine
Atlanta, Georgia

William Zev Rymer, M.D., Ph.D.
Shirley Ryan AbilityLab
Chicago, Illinois

Gordon S. Mitchell, Ph.D.
University of Florida
Gainesville, Florida

Heather B. Hayes, Ph.D.
Emory University School of Medicine
Atlanta, Georgia

Randy D. Trumbower, P.T., Ph.D.
Harvard Medical School
Boston, Massachusetts
and
Spaulding Rehabilitation Hospital
Boston, Massachusetts

ORCID IDs: 0000-0002-5201-8603 (I.V.); 0000-0002-2282-9974 (R.D.T.).

*Corresponding author (e-mail: ivivodtzev@partners.org).

References

1. Trumbower RD, Jayaraman A, Mitchell GS, Rymer WZ. Exposure to acute intermittent hypoxia augments somatic motor function in humans with incomplete spinal cord injury. *Neurorehabil Neural Repair* 2012;26:163–172.
2. Hayes HB, Jayaraman A, Herrmann M, Mitchell GS, Rymer WZ, Trumbower RD. Daily intermittent hypoxia enhances walking after chronic spinal cord injury: a randomized trial. *Neurology* 2014;82: 104–113.
3. Trumbower RD, Hayes HB, Mitchell GS, Wolf SL, Stahl VA. Effects of acute intermittent hypoxia on hand use after spinal cord trauma: a preliminary study. *Neurology* 2017;89:1904–1907.
4. Fields DP, Mitchell GS. Spinal metaplasticity in respiratory motor control. *Front Neural Circuits* 2015;9:2.
5. Huxtable AG, Smith SM, Peterson TJ, Watters JJ, Mitchell GS. Intermittent hypoxia-induced spinal inflammation impairs respiratory motor plasticity by a spinal p38 MAP kinase-dependent mechanism. *J Neurosci* 2015;35:6871–6880.
6. Sankari A, Vaughan S, Bascom A, Martin JL, Badr MS. Sleep-disordered breathing and spinal cord injury: a state-of-the-art review. *Chest* 2019; 155:438–445.
7. Cohen J. Statistical power analysis for the behavioral sciences. New York, NY: Lawrence Erlbaum Associates; 1988.
8. Peng YJ, Overholt JL, Kline D, Kumar GK, Prabhakar NR. Induction of sensory long-term facilitation in the carotid body by intermittent hypoxia: implications for recurrent apneas. *Proc Natl Acad Sci USA* 2003;100:10073–10078.
9. Lovett-Barr MR, Satriotomo I, Muir GD, Wilkerson JE, Hoffman MS, Vinit S, *et al*. Repetitive intermittent hypoxia induces respiratory and somatic motor recovery after chronic cervical spinal injury. *J Neurosci* 2012;32:3591–3600.
10. Navarrete-Opazo A, Alcayaga J, Sepúlveda O, Rojas E, Astudillo C. Repetitive intermittent hypoxia and locomotor training enhances walking function in incomplete spinal cord injury subjects: a randomized, triple-blind, placebo-controlled clinical trial. *J Neurotrauma* 2017;34:1803–1812.

A Unique Case of Secondary Pulmonary Alveolar Proteinosis after E-Cigarette, or Vaping, Product Use–associated Lung Injury

To the Editor:

Clinical, radiographic, and histopathologic criteria continue to emerge in cases of e-cigarette, or vaping, product use–associated lung illness (EVALI) (1, 2). We report a unique case of EVALI with radiographic, cytologic, and electron microscopy (EM) findings most consistent with secondary pulmonary alveolar proteinosis (PAP).

A 20-year-old female patient with chronic tetrahydrocannabinol (THC) vape use presented to the emergency room with 10 days of progressive dyspnea and cough. Her past medical history was significant for major depressive and anxiety disorder since 2015. She had no prior medical history of recurrent respiratory symptoms or prior diagnosis of chronic respiratory disease. She admitted to vaping counterfeit THC-based e-cigarette cartridges daily (50–100 puffs/d) for over a year. More specifically, she admitted purchasing THC-based cartridges from a friend that often did not have standardized labeling, strongly suggestive of noncertified or counterfeit production. She also reported inhaling marijuana using a water pipe with "dabs" on a bong nail as well as regular alcohol use (1–2 drinks

Table 1. Laboratory Workup at Initial Presentation

Laboratory Test	Result	Reference Values
CRP, mg/L	178	0–10
ESR, mm/h	70	0–20
LD, U/L	904	118–225
Platelets, $\times 10^9$/L	377	160–370
WBC, $\times 10^9$/L	20.9	4.0–10.0
Neutrophils, $\times$1,000/μl	18.2	1.6–6.1
Lymphocytes, $\times$1,000/μl	1.3	1.2–3.7
Hb, g/dl	10.7	11.2–15.7
Hct, %	33	34–45
BUN, mg/dl	12	6–20
Creatinine, mg/dl	0.5	0.5–1.0
Sodium, mmol/L	134	133–145
Postassium, mmol/L	2.9	3.3–5.1
Chloride, mmol/L	94	96–108
Cultures	Negative	NA

Definition of abbreviations: BUN = blood urea nitrogen; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Hct = hematocrit; LD = lactate dehydrogenase; NA = not applicable; WBC = white blood cell count.

Originally Published in Press as DOI: 10.1164/rccm.202002-0252LE on May 11, 2020