Effects of acute intermittent hypoxia on hand use after spinal cord trauma

A preliminary study

Randy D. Trumbower,
PT, PhD
Heather B. Hayes, PhD
Gordon S. Mitchell, PhD
Steven L. Wolf, PT, PhD
Victoria A. Stahl, PhD

Correspondence to
Dr. Trumbower:
rtrumbower@partners.org

ABSTRACT

Objective: To test the hypothesis that daily acute intermittent hypoxia (AIH) combined with hand opening practice improves hand dexterity, function, and maximum hand opening in persons with chronic, motor-incomplete, cervical spinal cord injury.

Methods: Six participants completed the double-blind, crossover study. Participants received daily (5 consecutive days) AIH (1.5 episodes per day: 1.5 minutes of fraction of inspired oxygen [FI_{O_2}] = 0.09, 1-minute normoxic intervals) followed by 20 repetitions of hand opening practice and normoxia (sham, FI_{O_2} = 0.21) + hand opening practice. Hand dexterity and function were quantified with Box and Block and Jebsen-Taylor hand function tests. We also recorded maximum hand opening using motion analyses and coactivity of extensor digitorum and flexor digitorum superficialis muscles using surface EMG.

Results: Daily AIH + hand opening practice improved hand dexterity, function, and maximum hand opening in all participants. AIH + hand opening practice improved Box and Block Test scores vs baseline in 5 participants ($p = 0.057$) and vs sham + hand opening practice in all 6 participants ($p = 0.016$). All participants reduced Jebsen-Taylor Hand Function Test (JTHF) time after daily AIH + hand opening practice (-7.2 ± 1.4 seconds) vs baseline; 4 of 6 reduced JTHF time vs sham + hand opening practice ($p = 0.078$). AIH + hand opening practice improved maximum hand aperture in 5 of 6 participants (8.1 ± 2.7 mm) vs baseline ($p = 0.018$) and sham + hand opening practice ($p = 0.030$). In 5 participants, daily AIH-induced changes in hand opening were accompanied by improved EMG coactivity ($p = 0.029$).

Conclusions: This report suggests the need for further study of AIH as a plasticity “primer” for task-specific training in spinal cord injury rehabilitation. Important clinical questions remain concerning optimal AIH dosage, patient screening, safety, and effect persistence.

ClinicalTrials.gov identifier: NCT01272336. *Neurology*® 2017;89:1904–1907

GLOSSARY

AIH = acute intermittent hypoxia; **BBT** = Box and Block Test; **BDNF** = brain-derived neurotrophic factor; **cSCI** = cervical spinal cord injury; **JTHF** = Jebsen-Taylor Hand Function Test.

Restoring hand function is critical in persons with cervical spinal cord injury (cSCI). Breathing mild bouts of low oxygen (acute intermittent hypoxia [AIH]) is a promising treatment to improve motor function after cSCI. AIH elicits serotonin- and brain-derived neurotrophic factor (BDNF)–dependent motor plasticity within somatic motor nuclei in rats.¹ Combined daily AIH + ladder walking improves forelimb placement during ladder walking in rats with cSCI,² and daily AIH + walking practice increases walking speed and endurance in humans with incomplete SCI.^{3,4} Here, we demonstrate initial evidence that daily AIH + hand opening practice enhances hand function in persons with chronic cSCI.

METHODS Participants. Six persons with motor-incomplete cSCI, as defined with International Standards for Neurological Classification of Spinal Cord Injury,⁵ participated in the study (table). Participants had traumatic injuries, no joint contractures,

From the Department of Physical Medicine and Rehabilitation (R.D.T.), Harvard Medical School, Cambridge; Department of Physical Medicine and Rehabilitation (R.D.T.), Spaulding Rehabilitation Hospital, Charlestown, MA; Division of Physical Therapy (H.B.H., S.L.W., V.A.S.), Department of Rehabilitation Medicine, Emory University School of Medicine, Atlanta, GA; Center for Respiratory Research and Rehabilitation (G.S.M.), Department of Physical Therapy, and McKnight Brain Institute (G.S.M.), University of Florida, Gainesville; and Center for Visual and Neurocognitive Rehabilitation (S.L.W.), Atlanta VA Medical Center, Decatur, GA.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Table Baseline demographics and clinical characteristics

Participant	Age, y	Sex	Treatment order	LOI/AIS grade	Injury type	Time since injury, y	UEMS (R)	Spasticity/pain medication
S1	55	M	Sham/AIH	C5/C	Trauma	40	16	None
S2	28	M	AIH/sham	C5/D	Trauma	9	22	Valium (PRN)
S3	44	M	Sham/AIH	C5/C	Trauma	8	22	Gabapentin
S4	33	M	AIH/sham	C5/C	Trauma	3	22	Baclofen
S5	43	M	AIH/sham	C5/D	Trauma	16	16	None
S6	56	M	AIH/sham	C5/D	Trauma	38	23	None
Mean ± SEM	43 ± 5					19 ± 1	20 ± 1	

Abbreviations: AIH = acute intermittent hypoxia; AIS = American Spinal Cord Injury Association Impairment Scale; LOI = level of injury; PRN = as necessary; R = right (dominant) arm; UEMS = upper extremity motor scores.

voluntary finger movements, and ability to follow commands. Persons with brain injury, cardiopulmonary complications, or other serious medical conditions were excluded. The Emory University Institutional Review Board approved the study, which is registered with ClinicalTrials.gov (NCT01272336).

Safety monitoring. We monitored cardiorespiratory function (GE Dash 4000 Monitor, Chicago, IL) throughout the protocols to ensure that heart rate (40–160 bpm), systolic blood pressure (85–160 mm Hg), and oxyhemoglobin saturation (>75%) remained within safe limits.³ We also monitored pain, dizziness, distress, autonomic dysreflexia, and mental function before, during, and after treatment.

Protocols. Participants received daily (5 consecutive days) AIH (15 episodes per day: 1.5 minutes of fraction of inspired oxygen [FI_{O_2}] = 0.09, 1-minute normoxic intervals)³ followed by 20 repetitions of hand opening practice and normoxia (sham, FI_{O_2} = 0.21) + hand opening practice. Treatments were randomized with 2-week minimum washout periods. We delivered AIH with a gas mixing system (HYP-123, Hypoxico Inc, New York, NY) and nonrebreathing mask as reported previously.^{1,3} Inspired oxygen concentrations were monitored continuously (OM-25RME, Maxtec Inc, Salt Lake City, UT).

Hand assessment. We assessed hand function using 2 clinical outcome measures with high interrater and intrarater reliability: the Box and Block Test (BBT)⁶ quantified hand dexterity, and the Jebsen-Taylor Hand Function Test (JTHF)⁷ quantified hand use during daily-living activities.

As secondary outcome measure, we quantified maximum hand opening using 2 optical motion analyses systems (Northern Digital, Waterloo, Ontario, Canada) with infrared light-emitting diodes on the first fingernail and thumbnail (figure).⁸ We instructed individuals to place their hand on a wooden ball (diameter = 7.6 cm) while resting their forearm on a pad. On a visual go signal, participants maximally opened the hand for 3 seconds while the palm maintained ball contact (10 trials with 30 seconds of rest between trials). We acquired kinematic data at 100 Hz.

During maximum hand opening, we also recorded surface EMG from extensor digitorum and flexor digitorum superficialis muscles normalized to maximum voluntary contractions.⁸ The extensor digitorum and flexor digitorum superficialis represented agonist and antagonist extrinsic hand muscles active during hand opening. EMG signals were amplified (AMT-16, Bortec Biomedical, Calgary, Alberta, Canada), low-pass filtered at 500 Hz, sampled at 2.5 kHz (PCI-6289, National Instruments, Austin, TX), and collected with custom software (Matlab xPC, MathWorks,

Inc, Natick, MA). Coactivity ratios were calculated to assess changes in muscle coordination during maximum opening.⁸

Statistical analyses. We used a randomized, double-blinded crossover design to test our hypotheses that daily AIH + hand opening practice enhances hand dexterity (BBT, seconds), function (JTHF, seconds), and maximum hand opening. We assessed differences from baseline and between treatments via Wilcoxon rank-sum tests. Using the Holm-Bonferroni method,⁹ we corrected for multiple between-group comparisons. Corrected *p* values were considered significant at *p* < 0.05. Mean differences from baseline reported as means ± standard error.

RESULTS Results reported in this study are not part of a larger ongoing trial. Daily AIH + hand opening practice improved hand dexterity, function, or opening in all participants (figure). AIH + hand opening practice improved BBT scores vs baseline in 5 participants (*p* = 0.057) and vs sham + hand opening practice in all 6 participants (*p* = 0.016). All participants reduced JTHF time after daily AIH + hand opening practice (-7.2 ± 1.4 seconds) vs baseline; 4 of 6 reduced JTHF time vs sham + hand opening practice (*p* = 0.078). AIH + hand opening practice improved maximum hand aperture in 5 of 6 participants (8.1 ± 2.7 mm) vs baseline (*p* = 0.018) and sham + hand opening practice (*p* = 0.030). In 5 participants, daily AIH-induced changes in hand opening were accompanied by improved EMG coactivity (*p* = 0.029); sham + hand opening practice had no effect vs baseline activity (*p* = 0.606).

Daily AIH + hand opening practice was well tolerated by all participants, with no adverse events reported. We found no differences in heart rate, blood pressure, oxyhemoglobin saturation, or cognitive function (Mini-Mental State Examination) before vs after 5 consecutive days of AIH + hand opening practice (all *p* > 0.05).

DISCUSSION We demonstrate that daily AIH + hand opening practice enhances hand function in persons with chronic cSCI, extending earlier reports of improved respiratory function in rodents² and leg

(A, B, D, and F) Box-whisker plots represent 95% confidence intervals relative to mean (horizontal black line). Vertical error bars indicate SD. Asterisks correspond to statistical significance after post hoc Holm-Bonferroni correction. Color dots represent results from individual participants. (A and B) Effects of daily (5 consecutive days) AIH + HOP (white) vs sham + HOP (gray) on clinical measures of hand dexterity (BBT) and speed (JTHF) tests relative to BL. (C) During hand opening, maximum hand aperture (A_{max}) quantified by recording distance between LEDs of finger and thumb (black circles) with 3-dimensional motion capture system and corresponding activity of ED and FDS muscles recorded with EMG via standard dual surface electrodes (white circles). (E) Mean (black trace) $\pm$ SD (gray traces) of representative participant (S01) during hand opening (top) with corresponding EMG recordings (bottom). (F) Change in ED and FDS coactivity at A_{max} after AIH + HOP. AIH = acute intermittent hypoxia; BBT = Box and Block Test; BL = baseline; cSCI = cervical spinal cord injury; ED = extensor digitorum; FDS = flexor digitorum superficialis; HOP = hand opening practice; JTHF = Jebsen-Taylor Hand Function Test; LED = light-emitting diodes; MVC = maximum voluntary contraction.

function in humans.³ Hand dexterity (BBT and JTHF) was particularly sensitive to daily AIH + hand opening practice. This observation may reflect the combinatorial effect of AIH with task-specific training similar to task-specific benefits of AIH and walking practice.³ Improved hand opening in 5 of 6 participants was accompanied by changes in muscle coordination, suggesting that daily AIH + hand opening practice may fine-tune muscle activation in a task-appropriate manner. Repetitive AIH may elicit synergistic benefits with AIH + task-specific training after SCI. In rodents, BDNF and its high-affinity receptor (TrkB) are necessary

and sufficient for AIH-induced motor plasticity within relevant motor nuclei¹ and are similarly up-regulated in other forms of training and task practice. Similarly, upregulation of BDNF mRNA via motor training is associated with functional recovery in rodents after SCI.¹⁰ We hypothesize that AIH + task-specific training also may result in beneficial BDNF/TrkB signaling in humans; however, this possibility remains unknown.

Despite these exciting preliminary findings, the study has limitations. The small sample size reduced statistical power and prevented analyses of differences in user responsiveness based on injury severity

(e.g., upper extremity motor scores), time since injury, and medication use. Although participants had a minimum washout period of 2 weeks, we cannot fully exclude carryover effects from daily AIH or hand movement practice to the subsequent sham protocol. Future large-scale trials should consider stratified populations according to function or injury level without crossover to limit confounds. Finally, we did not assess AIH and sham or sham effects without hand practice; thus, the extent to which AIH alone enhances hand function remains unclear. This report suggests need for further study of AIH as a plasticity primer for task-specific training in SCI rehabilitation.

AUTHOR CONTRIBUTIONS

Randy D. Trumbower, PT, PhD, was the principal investigator for this study. He contributed to development of study concept and design, as well as data analyses and interpretation, literature search, figure, and manuscript revisions. As corresponding author, he has full access to all data and final responsibility for the decision to submit for publication. Heather B. Hayes, PhD, and Victoria A Stahl, PhD, contributed to study design, participant recruitment, data collection, analyses, and interpretation. Drs. Trumbower, Hayes, and Stahl also performed statistical analyses (with consultation from biostatistician Michael Epstein, PhD), wrote the first draft of manuscript, and contributed to manuscript revisions and approval of final submission. Drs. Trumbower, Hayes, and Stahl contributed to participant recruitment, screening, blind rating, data collection and analyses, and approval of final submission. Gordon S. Mitchell, PhD, and Steven L. Wolf, PT, PhD, contributed to development of study concept and design, as well as data interpretation, literature search, figure, and manuscript revisions and approval of final submission.

ACKNOWLEDGMENT

The authors thank Karly Bishop, DO, for her assistance with participant recruitment, screening, and blind rating; Jonathan Albert, MD, Ian Cooke, MD, and Matthew Freeman, MD, for assistance with data collection; and Michael Epstein, PhD, for assistance with statistical analyses. They also thank members of the Data Safety and Monitoring Board, particularly Dale Strasser, MD. They extend special thanks to all study participants.

STUDY FUNDING

This study was supported through the Craig H. Neilsen Foundation (163907) and NIH NINDS (K12 HD055931). The funding sources had no role in study design, collection, patient recruitment, or interpretation of data.

DISCLOSURE

R. Trumbower received research support for this preliminary study from the Craig H. Neilsen Foundation and NIH National Institute of Neurological Disorders and Stroke. H. Hayes, M. Gordon, S. Wolf, and V. Stahl report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received March 9, 2017. Accepted in final form August 16, 2017.

REFERENCES

1. Baker-Herman TL, Fuller DD, Bavis RW, et al. BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. *Nat Neurosci* 2004;7:48–55.
2. Lovett-Barr MR, Satriotomo I, Muir GD, et al. Repetitive intermittent hypoxia induces respiratory and somatic motor recovery after chronic cervical spinal injury. *J Neurosci* 2012;32:3591–3600.
3. 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.
4. Navarrete-Opazo A, Alcayaga J, Sepulveda 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.
5. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International Standards for Neurological Classification of Spinal Cord Injury (revised 2011). *J Spinal Cord Med* 2011;34:535–546.
6. Platz T, Pinkowski C, van Wijck F, Kim IH, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer test, Action Research Arm Test And box and Block Test: a multicentre study. *Clin Rehabil* 2005;19:404–411.
7. Jebson RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. *Arch Phys Med Rehabil* 1969;50:311–319.
8. Stahl VA, Hayes HB, Buetefisch CM, Wolf SL, Trumbower RD. Modulation of hand aperture during reaching in persons with incomplete cervical spinal cord injury. *Exp Brain Res* 2015;233:871–884.
9. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979;6:65–70.
10. Gomez-Pinilla F, Huie JR, Ying Z, et al. BDNF and learning: evidence that instrumental training promotes learning within the spinal cord by up-regulating BDNF expression. *Neuroscience* 2007;148:893–906.