# Hypoxic locomotor rehabilitation for incomplete spinal cord injury

## Not an oxymoron

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*Neurology*® 2014;82:98–99

Neurorehabilitation is experiencing a paradigm shift toward treatments that are both effective and efficient, driven by increasing demands upon clinical practice and the staggering burden of health care expenditures. The impetus is toward finding ways to maximize the potential for recovery by targeting networks spared by the lesion. Residual networks can undergo reorganization with recovery, involving plasticity or improved efficiency at the level of preexisting synapses and sprouting from surviving fibers for creation of new circuits.[1] Capitalizing on the potential for plasticity and employing methods that can augment this potential are the 2 driving themes in current rehabilitation research. In this issue of *Neurology*®, Hayes et al.[2] present a study that sought to address both.

The authors introduced a unique strategy to harness plasticity in spared networks in patients with incomplete spinal cord injury (SCI) to aid locomotor rehabilitation. This unconventional paradigm involved daily intermittent hypoxia delivered over 5 days. Patients with incomplete SCI (C2-T2) received 15 90-second periods of hypoxia alternating with 60 seconds of normoxia, for a total of 37.5 minutes each day. Hypoxia involved breathing air containing low concentrations of oxygen (10%) via a nonrebreathing mask, while normoxic air contained the usual 21% oxygen. Two separate studies were conducted, each using a randomized, blinded, crossover controlled design. One study examined whether daily acute intermittent hypoxia was effective in promoting walking speed and endurance compared to sham; the second study evaluated whether the combination of hypoxia with walking, initiated within 60 minutes of hypoxia, was more favorable than walking paired with sham. Patients walked for 30 minutes at maximum sustainable exertion. Crossover between hypoxia and sham occurred at least 2 weeks after the end of the first treatment. With 5 daily sessions of hypoxia, patients showed improvement in speed, while the combination of hypoxic therapy with subsequent walking training generated large effect sizes for endurance. Overall, pairing of hypoxia with walking showed clinically meaningful changes in speed in 30% and in endurance in >70% of patients.

The unique nature of the protocol raises several questions. How does a treatment that requires individuals to inhale low concentrations of oxygen really help locomotor function, let alone in those with compromised respiratory and motor capacity? Plausible mechanisms were addressed previously in translational work.[3,4] In rat models, acute hypoxic episodes enhance respiratory and forelimb motor capacities in association with spinal plasticity below the level of lesion. The signatures of plasticity include greater expression of trophic proteins in the phrenic motor neurons (C4, diaphragmatic muscles) and in those supplying forelimb muscles (C7).[3] The trigger may be hypoxia-induced release of spinal serotonin,[5] which sets off a cellular cascade enhancing changes in proteins subserving respiratory and motor plasticity. Other unexplored mechanisms could include induction of the hypoxia-inducible factor–vascular endothelial growth factor (HIF-VEGF) signaling cascade, known to be triggered by hypoxia, which influences posttraumatic neural repair and plasticity.[6] Another obvious question is whether the technique is safe and clinically feasible. The authors emphasize that their use of acute rather than chronic hypoxia was associated with no clinical signs of respiratory or cardiac distress or emergent paroxysmal autonomic response (dysreflexia) that can occur in individuals with lesions above T6.

As the first clinical evaluation of its kind, key questions remain to be addressed before the technique can be translated into practice. The mechanism of benefit, while partially defined in animals, is unexamined in humans. Do benefits purely involve spinal plasticity or are they partially explained by improved cardiorespiratory function, or perhaps a greater capacity to tolerate fatigue? Are these mechanisms analogous to mechanisms of improved exercise performance in competitive athletes undergoing high-altitude hypoxic training? Is spinal plasticity leading or following systemic cardiovascular, erythropoietic, and adaptive muscle response triggered by hypoxia? Methods to study

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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 editorial.

spinal network reorganization and voluntary activation in gait (as opposed to pulmonary function and cardiorespiratory conditioning) may help dissociate the underlying processes. Are the results generalizable? All except 2 patients in the study were American Spinal Injury Association grade D (most highly functioning incomplete SCI); are beneficial effects only possible in a restricted subpopulation with little damage to phrenic and somatomotor networks and the ability to ability maximally exert in aerobic activities?[7] If the effect emerges purely from spinal plasticity below the lesion level, then would benefits occur for patients with injuries well below C2-T2, without compromise to respiratory neurons? Is the proposed treatment feasible? Is intermittent hypoxia best implementable as "plasticity-promoting primers" (in the authors' words) in clinical settings or would it ever be translatable to community- or home-based programs? As the authors report, benefits of 5 daily sessions are maintained over only a couple of weeks; dosing then becomes clinically relevant since a balance between maximizing and retaining benefits is important, especially if there are potential safety risks.

Hayes et al.[2] present high-quality evidence in support of a novel potential treatment, which has promise compared to other contemporary methods of gait rehabilitation. The effect was observed using a randomized controlled crossover design that is challenging to implement in rehabilitation research. It requires adequate washout, baseline equivalence, and stability of measurements. To expedite clinical acceptance of promising new approaches such as the one presented here, a comprehensive evaluation of evidence that includes case studies, focus groups, and program evaluations may be meaningful.[8] As the utility of promising contemporary locomotor rehabilitation that promotes spinal plasticity, such as treadmill training, is being questioned due to its cost-restrictive and resource-intensive nature,[8] the initiative of Hayes et al. to maximize outcomes of standard rehabilitation by priming it with strategies shown to promote plasticity aligns with demands to improve efficiency. For future clinical application, studies need to investigate other outcome measures, the balance between dose and safety, the feasibility of delivery, and the proposed mechanisms of action in humans. The work by Hayes et al.[2] is an excellent step from a clinical translational perspective.

## AUTHOR CONTRIBUTIONS

Ela Plow: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Michael G. Fehlings: drafting/revising the manuscript, study concept or design, study supervision, obtaining funding.


## STUDY FUNDING

No targeted funding reported.


## DISCLOSURE


E.B. Plow is supported by the Department of Defense/US Army's Medical Research and Materiel Command, American Heart Association, and NIH K01HD069504. M.G. Fehlings is supported by the Gerald and Tootsie Halbert Chair in Neural repair and Regeneration and receives grant support from the Canadian Institutes of Health Research, the Christopher and Dana Reeve Foundation, AOSpine, and the Wings for Life Foundation. Go to Neurology.org for full disclosures.


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