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Isabelle Vivodtzev, Anthony Napolitano, Glen Picard, J. Andrew Taylor. Ventilatory support during whole-body row training improves oxygen uptake efficiency in patients with high-level spinal cord injury: A pilot study. *Respiratory Medicine*, 2020, 171, pp.106104 -. 10.1016/j.rmed.2020.106104 . hal-03492353

**HAL Id: hal-03492353**

**<https://hal.science/hal-03492353>**

Submitted on 22 Aug 2022

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## **Ventilatory support during whole-body row training improves oxygen uptake efficiency in patients with high-level spinal cord injury: a pilot study**

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**Funding:** Support for this study was provided by NIH Grants (R01-HL-117037 and R21-HD-088891), USA. IV was supported by “Fondation de la recherche médicale”, France and the Ellen R. and Melvin J. Gordon Center for the Cure and Treatment of Paralysis, USA

## **Abstract**

High-level spinal cord injury (SCI) is characterized by profound respiratory compromise. One consequence is a limitation of whole-body exercise-based rehabilitation, reducing its cardioprotective effect. We investigated the use of ventilatory support during training on cardiorespiratory response to exercise.

Nine subjects with high-level SCI (T3-C4) were included in this double-blind sham-controlled study. All had training adaptations plateauing for more than 6 months before enrolling in the study. After performing baseline assessment, participants were randomly assigned to continue training with non-invasive ventilation (NIV: n = 6: IPAP =  $20 \pm 2$ , EPAP: 3 cmH<sub>2</sub>O) or sham (n = 3: IPAP = 5, EPAP: 3 cmH<sub>2</sub>O) for 3 months and performed again maximal exercise tests. We compared the oxygen uptake efficiency slope (OUES, the rate of increases in VO<sub>2</sub> in relation to increasing VE) before and after training.

Training with NIV increased OUES both compared to baseline ( $4.1 \pm 1.1$  vs.  $3.4 \pm 1.0$ , i.e.  $+20 \pm 12\%$ ,  $p < 0.05$ ) and Sham ( $p = 0.01$ ), representing an increase in ability to uptake oxygen for a given ventilation. This result was sustained without NIV during the test, suggesting improved cardiopulmonary reserve. Best responders were the youngest whose characteristics were very similar to sham participants. In addition, NIV tended to increase weekly rowing distance by 24% ( $p = 0.09$ , versus 10% in sham).

Our results are very suggestive of a positive effect of ventilatory support during whole-body exercise in high-level SCI. Training adaptations found are of great importance since this sub-population of patients have the greatest need for exercise-based cardio-protection.

## Introduction

Spinal cord injury (SCI)<sup>1</sup> is characterized by profound respiratory compromise usually proportional to the level of injury. Those with injuries above T3 have the most profound loss[1] with a rapid and shallow breathing pattern during exercise that impairs gas exchange[2]. One consequence of this pulmonary constraint is a limitation to whole-body exercise-based rehabilitation, reducing its cardioprotective effect. Indeed, whole-body exercise requires higher cardiopulmonary demand than arms-only exercise in SCI. While the respiratory system can adequately meet the demands of arms-only exercise, even after training[3], exercise that also engages the paralyzed muscle such as hybrid functional electrical stimulation (FES) rowing[4] results in greater whole-body skeletal muscle demand. In those with high-level SCI, whole-body exercise results in skeletal muscle demand that can exceed ventilatory capacity[5]. We reasoned that external ventilatory support could overcome pulmonary limitation to whole-body FES row training, allowing for increased ability to train and greater training-induced adaptations in high-level SCI. In a previous study, we reported that acute utilization of bi-level non-invasive ventilation (NIV) during maximal FES-row exercise led to a more advantageous respiratory pattern (slower and deeper breathing) in these patients, resulting in improved oxygen uptake efficiency slope (OUES), an index of cardiopulmonary improvement[6]. In the present study, we present the effect of a 3-month FES-row training program with NIV that results in changes in oxygen uptake efficiency.

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<sup>1</sup> **Abbreviation list:** EPAP, expiratory positive airways pressure; FES, functional electrical stimulation; IPAP, inspiratory positive airways pressure; OUES, oxygen uptake efficiency slope ; NIV, non-invasive ventilation ; SCI, spinal cord injury; VE, minute ventilation; VO<sub>2</sub>, oxygen consumption

## Material and methods

In a randomized double-blind sham-controlled study, eleven individuals with high-level SCI (T3-C4) were enrolled from an outpatient rehabilitation program after  $4 \pm 2$  years of regular training with whole-body hybrid FES-rowing. All had training adaptations plateauing for more than 6 months and had completed our previous study comparing the acute effect of NIV vs. sham during maximal exercise testing with FES-rowing[6]. The test performed in the sham condition constituted the baseline for the present study. After baseline, participants were randomly assigned to continue training with NIV ( $n = 6$ : IPAP =  $20 \pm 2$ , EPAP: 3 cmH<sub>2</sub>O) or sham ( $n = 5$ : IPAP = 5, EPAP: 3 cmH<sub>2</sub>O) for 3 months and performed again maximal exercise tests (in both sham and NIV conditions). Two patients from the sham group dropped out during the first month of training for medical reasons (neurological pain) unrelated to the study. Patient characteristics and respiratory function were similar between groups (Table 1). Signed consent was obtained from each participant and the study is registered on clinicaltrials.gov number (NCT02865343). Aerobic efficiency was assessed during incremental maximal exercise before and after training using a computer-assisted open circuit spirometry (Innocor, Innovision, Odense, Denmark) as previously described[6]. Expired gas analysis (Innocor) and heart rate monitor (Suunto, Valimotie 7, Vantaa, Finland) were performed throughout the test. At the end of the test, a fingertip blood sample was obtained for peak lactate assessment (Lactate Plus, Nova Biomedical, Waltham MA). Because four participants did not reach peak exercise criteria, we used OUES as a substitute of peak oxygen consumption ( $VO_{2\text{peak}}$ ) [6]. OUES was calculated as:  $VO_2 = \text{OUES} \times \log_{10} \text{VE} + \text{constant}$ . It represents the rate of increases in  $VO_2$  in relation to

increasing VE. A steeper slope indicates greater oxygen uptake for a given amount of ventilation[7]. We used Wilcoxon rank test for within-group comparison and two-ways repeated measure of ANOVA for between-group comparison. Data are presented in Mean  $\pm$  SD.

## Results

Training with NIV increased OUES both compared to baseline ( $4.1 \pm 1.1$  vs.  $3.4 \pm 1.0$ , i.e.  $+20 \pm 12\%$ ,  $p < 0.05$ ) and sham ( $p = 0.01$ , Figure 1) while no change was found in sham ( $1.8 \pm 0.3$  vs.  $2.1 \pm 0.8$ , after vs. before respectively). This result was found without NIV during the final test. Adding NIV during the final test did not provide additional improvement in OUES ( $4.1 \pm 1.5$  and  $2.0 \pm 0.7$ , in NIV and Sham respectively). Moreover, the best responders to training with NIV were the youngest whose characteristics were very similar to sham participants in age, level of injury and time since injury (participants #1-3 vs. #7-9, Table 1), reinforcing the plausibility of the results. In participants with reliable measures of  $VO_2$ peak, we also found a homogeneous improvement in  $VO_2$ peak in those using NIV ( $+0.21 \pm 0.04$  L/min) while the response was, again, randomly changed in the sham group ( $+0.08 \pm 0.10$  L/min). Furthermore, power output tended to increase after training with NIV ( $+9 \pm 13$  Watt,  $p = 0.15$ ,  $n = 6$ ) vs. no change with Sham ( $0 \pm 8$  Watt,  $n = 3$ ). Improvement in OUES was associated with an overall reduction in peak breathing frequency after training with NIV while it tended to increase with Sham ( $-3 \pm 6$  [range: from 33-52 to 30-38 bpm] vs.  $+4 \pm 8$  [range: from 33-46 to 35-51 bpm],  $p = 0.19$ ). Peak tidal volume was unchanged in both groups. Although non-significant, this tendency suggests a change towards a more advantageous respiratory pattern in NIV, as we previously found in our study with acute NIV[6]. Interestingly, we found that peak  $SpO_2$  ranged between 94% and 99% without

differences between groups, but there was a slight drop in  $VD/VT$  in the NIV group from  $0.24 \pm 0.09$  to  $0.22 \pm 0.06$  which was not found in the sham group, suggesting improvement in OUES was related to improved alveolar ventilation rather than change in oxygen delivery. Lastly, subjects in the NIV group tended to increase weekly rowing distance by 24% ( $p=0.09$ , versus 10% in sham), suggesting increased ability to train with NIV. After training, the subjective reason for fatigue at the end of the maximal test was “exhaustion” ( $n=4/6$ ) or “breathing” ( $n=2/6$ ) in NIV group while it was consistently “arms fatigue” ( $n=3/3$ ) in sham. Interestingly, this was associated with a trend to increased ventilatory threshold during maximal exercise in NIV only ( $22 \pm 11$  vs.  $21 \pm 9$  mL/min/kg after vs. before training).

## **Discussion**

Our results suggest that training with NIV can improve oxygen uptake efficiency during whole-body hybrid FES-rowing in high-level SCI. This improvement represents an increase in the ability to uptake oxygen for a given ventilation that is sustained without assisted ventilation, suggesting improved cardiopulmonary reserve. This training adaptation is of great importance to those patients who had plateaued in their aerobic capacity despite continued regular training as we previously reported[5, 8]. Moreover, NIV was associated with an increased ability to train.

We can only speculate on mechanisms for the improvement in OUES. One might be an increase in respiratory afferent input during exercise while using NIV. The propriospinal network located throughout the cervical and thoracic cord can control inspiratory muscle activity[9]. Hence, increasing tidal volume during exercise via NIV may activate local spinal circuits as well as

spinobulbar-spinal circuits that relay proprioceptive information to the spinal cord and/or to the brainstem, leading to a permanent change in the pattern of breathing, for example, via longer inspiratory time[10]. Interestingly, a positive response to NIV at baseline was not required for OUES to improve after training, and in fact a positive response to training with NIV was seen despite a negative acute response to NIV (Table 1). However, older subjects may present with stiffer lungs that are less able to respond to NIV during training, leading to lesser improvements in OUES after training. Furthermore, to allow a good efficacy of NIV during rowing, inspiratory pressure needs to be optimally titrated during the first sessions to reduce its impact on intrathoracic pressure and left-ventricular stroke volume. In addition, a good synchronization with the device may be challenging in some patients with high breathing frequency. Lastly, participants may have incomplete functionality of the hands, requiring someone to assist with the mask during training.

Although further studies are needed to confirm the impact and to pursue the mechanisms by which training with NIV may permanently increase oxygen uptake efficiency, the current work suggests it may be a valuable adjunct to whole-body hybrid FES training for cardiopulmonary improvement in high-level SCI.



**Table 1**

	Training group	Age (yrs.)	BMI (kg/m <sup>2</sup> )	Injury Level	ASIA score	TSI (yrs.)	Complete injury	Resting pulmonary function				Acute response to NIV at baseline
								FVC (L)	FEV <sub>1</sub> (L)	ERV (L)	IC (L)	
#1	NIV	21	21.8	C5	C	3	No	4.37	4.23	1.40	3.10	Yes
#2	NIV	27	31.0	C4	A	4	Yes	2.59	3.84	1.20	2.55	Yes
#3	NIV	45	28.1	T3	A	22	Yes	1.92	1.86	0.52	1.05	No
#4	NIV	50	17.5	C6	A	9	Yes	3.92	3.18	1.02	2.60	No
#5	NIV	55	42.7	C7	C	2	No	2.94	2.54	0.23	2.67	Yes
#6	NIV	59	21.7	C4	C	42	No	1.67	1.61	0.22	1.06	Yes
#7	Sham	25	25.2	C4	B	6	Yes	2.73	2.50	0.22	2.45	No
#8	Sham	28	27.8	C4	A	4	Yes	4.45	3.13	0.87	3.32	Yes
#9	Sham	40	35.2	T2	C	26	No	3.30	3.08	0.39	2.86	Yes

Definition of abbreviations: ASIA, American spinal injury association impairment scale; BMI, body mass index; ERV, Expiratory reserve volume; FEV<sub>1</sub>, Forced expiratory volume in one second; FVC, Forced vital capacity; IC, Inspiratory capacity; NIV, Non-invasive ventilation; TSI, Time since injury.

## Figure legend

**Figure 1:** Oxygen uptake efficiency slope as a measure of cardiopulmonary improvement during an incremental exercise test on FES-rowing after training with NIV (upper panel, grey sticks) or with sham NIV (lower panel, white sticks) in patients with high-level SCI. Testing were performed without assisted ventilation (without NIV). OUES was significantly increased in the NIV group, both when compared to baseline within-group values ( $p < 0.05$ ) and when compared to changes in the sham group ( $p = 0.01$ ).

### **CRedit authors statement**

**Isabelle Vivodtzev:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft; **Anthony Napolitano:** Investigation, Data Curation. **Glen Picard:** Methodology, Investigation. **J. Andrew Taylor:** Conceptualization, Supervision, Funding acquisition, Writing - Reviewing and Editing.

### **Acknowledgments**

The authors are grateful to the ExPD's team for their support during FES-rowing training and exercise tests. They also show gratitude to the National Institute of Health; the Ellen R. and Melvin J. Gordon Center for the Cure and Treatment of Paralysis, USA and the "Fondation de la recherche médicale", France for funding supports.

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Oxygen uptake  
efficiency slope

