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Lumbar Transcutaneous Electrical Nerve Stimulation to improve exercise performance in COPD patients

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ClinicalTrials.gov Identification Number: The protocol was prospectively registered on www.clinicaltrials.gov (NCT03312322).

Key Words: Chronic obstructive pulmonary disease; Exercise; Group III/IV muscle afferents; Transcutaneous electrical nerve stimulation; Fentanyl.

Short sentence: Lumbar transcutaneous electrical nerve stimulation aimed to block muscle group III-IV sensory afferents does not improve endurance exercise capacity in patients with chronic obstructive pulmonary disease.

To the Editor,

Muscle group III (Aδ fibres) and IV (C fibres) sensory afferents are involved in the cardiorespiratory adaptation to exercise (1, 2). Their inhibition with intrathecal fentanyl in the dorsal horn of spinal cord to block their cortical projections decreases high intensity constant workload endurance performance in healthy athlete subjects because of a blunted cardiorespiratory response to exercise. In this condition with high metabolic demand, any decrease in ventilation or hemodynamics would compromise performance because of a nearly maximal solicitation without any possibility for a compensatory strategy. At the opposite, Gagnon et al. have published that the use of spinal anesthesia with fentanyl with the goal of inhibiting muscle group III and IV fibres in COPD patients improved dyspnea and endurance capacity (3). This improvement was due to the blunted ventilatory response to exercise which improved physiological dead space, ventilatory efficiency and in turn, dyspnea. Moreover, at this relatively lower external workload compared with healthy subjects, cardiac output and peripheral oxygen extraction were not maximal and any mitigation in cardiac output (if any) would be overcome by an increase in peripheral muscle oxygen extraction (3). High frequency (HF) or low frequency (LF) transcutaneous electrical nerve stimulation (TENS) is a less invasive alternative that also activate opioid receptors, especially those located in the dorsal horn of the spinal cord (1, 4, 5). This approach deserves to be studied during exercise and over a course of pulmonary rehabilitation in these patients. We performed a randomized double-blind study (clinicaltrials.gov; NCT03312322) aimed to assess whether either HF or LF lumbar TENS could improve endurance exercise capacity in patients with COPD. Secondary objectives were to assess the influence of lumbar TENS on perceived exertion, ventilatory pattern and muscle oxygenation. We hypothesised that endurance capacity would be improved with lumbar TENS due to a blunted response in exercise ventilation which would contribute to improve ventilatory efficacy and reduce exercise dyspnoea. On the other hand, we hypothesised that any mitigation in cardiac output (if any) would be compensated by an increase in peripheral muscular oxygen extraction.

Consecutive subjects with severe stable COPD referred for pulmonary rehabilitation were screened for eligibility between October 2017 and October 2018. Inclusion criteria were patients aged ≥ 18 years and naive to TENS. Non-inclusion criteria were: contra-indication to TENS, opiate treatment during the previous three months and pregnancy. Twenty-five patients were screened: 12 did not met the inclusion criteria, 2 declined to participate, 1 recently used opiate treatment and 10 agreed to participate (and provided signed consent; approved by the French Ethics committee Est III (17.05.15)), which was the sample size chosen to gather preliminary data. Included patients performed three constant workload exercise testing (CWET; 75% of the maximal workload achieved during a previously performed incremental cardiopulmonary exercise testing (CPET)) up to exhaustion, with at least a 24h-rest period between tests, with either HF (100Hz, 100µs), LF (4Hz, 100µs) and sham TENS (100Hz, 100µs, intermittent placebo (6)) in a randomized order (computer-generated sequence and concealed allocation). TENS was set at rest, 10 min prior to each CWET and maintained throughout the test. The current was biphasic, symmetric and applied through four self-adhesive surface electrodes (5x5cm) positioned by pair at the L3-L4 level, 2cm laterally to the lower border of the corresponding vertebrae.

The intensity was adjusted just under the pain threshold every three minutes (and no longer increased during the CWET). Patients were told that they may no longer feel the current during the procedure due to accommodation (or the intermittent nature of the sham TENS)) but were asked not to discuss about their bodily sensations in order to maintain study blinding. Perceived exertion (dyspnoea and lower limb fatigue assessed every 30s using the Borg scale), gas exchanges and ventilatory pattern (including oxygen consumption and carbon dioxide production, recorded breath by breath (Vyntus CPX, Care Fusion, San Diego, CA) and muscle oxygenation (*vastus lateralis* muscle relative change in total haemoglobin and myoglobin (THb), oxyhaemoglobin and oxymyoglobin (HbO2) and deoxyhaemoglobin and deoxymyoglobin (HHb), continuously recorded at a frequency of 1Hz using a near-infrared spectroscopy device (NIRS; Portamon, Artinis, Einsteinweg, The Netherlands) and tissue O2 saturation (StO2), calculated as the ratio of HbO2/THb*100 and expressed as change from baseline, were monitored during the tests. Statistical analysis was performed using Prism 5 software and comparison between tests was performed using either repeated ANOVA and Tukey post hoc tests or Friedman and Wilcoxon post hoc test for pairwise comparison

according to the distribution. Secondary outcomes were analyzed both at time limit (Tlim) and at isotime. Isotime was defined as the Tlim of the shortest CWET.

Patients were 64 (IQR 57 to 67) years old, had severe bronchial obstruction (mean FEV1 (L): 0.9 (SD 0.3)), significant thoracic distension and decreased exercise capacity (median VO2 (ml/kg/min): 12.3 (IQR 11.2 to 18.7)). They all had a ventilatory limitation during the initial CPET. There was no significant difference in endurance capacity between LF, HF and sham TENS nor in dyspnoea or lower limb fatigue at isotime or time limit (Table 1). Gas exchanges and ventilatory patterns during exercise are shown in Table 1. NIRS data were not available in three patients, due to technical reasons. HbO2 was significantly different between LF, HF and sham TENS at isotime mainly due to a significant difference between LF and sham TENS ($p<0.05$). A similar trend was also observed at time limit ($p=0.06$). Finally, a trend toward an improved StO2 for LF TENS was also observed at time limit (Table 1).

Our study did not show any improvement in endurance exercise capacity with either HF or LF TENS. Overall metabolism and exercise ventilation tended to increase with LF TENS while NIRS revealed that local *rectus femoris* oxygenation tended to improve with both current. The lack of effects observed with HF TENS may be related to an activation of specific opioid receptor. While both the fentanyl and LF TENS activate the same μ-opioid receptors, HF TENS effects are mediated through the δ-opioid receptor (4). NIRS data are frequently used as an indirect surrogate for muscular oxygenation (7). Therefore, the present results suggest that TENS might improves the ratio between local oxygen delivery and consumption. Among potential mechanisms, an improvement in local oxygen supply through a TENS-mediated sympatho-vagal modulation, may improve vascular conductance and local blood flow (8). Alternatively, TENS may have change spatial recruitment (out of the range of the superficial NIRS area of interrogation) or the type of muscle fibres recruitment during exercise (9). A shift toward the recruitment of fast twitch muscular fibres (type II), which are energetically less efficient, would contribute to explain the concomitant increase in metabolism observed with LF TENS (10).

In conclusion, this study does not provide substantive clinical or physiological argument for a positive effect of lumbar TENS on exercise endurance capacity in stable COPD patients.

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Table 1. Impact of lumbar TENS on endurance exercise capacity and physiological parameters measured at isotime and time limit.

Variables	TENS settings			Between-group comparison
	Sham (n = 10)	High-frequency (n = 10)	Low-frequency (n = 10)	*p*
Endurance time *(s)*,				
Patient 1	377[#]	380	474	
Patient 2	122[#]	182	207	
Patient 3	124[#]	154	248	
Patient 4	147[#]	148	198	
Patient 5	250	143	104[#]	
Patient 6	442	427	367[#]	
Patient 7	278[#]	342	348	
Patients 8	341	302	271[#]	
Patients 9	225	162[#]	274	
Patient 10	491	202[#]	466	
Mean (SD)	280 (131)	244 (108)	296 (118)	0.25
Isotime				
Dyspnoea *(BORG)*, mean (SD)	5 (2)	6 (2)	5 (2)	0.59
Lower limb fatigue *(BORG)*, mean (SD)	5 (2)	6 (1)	5 (1)	0.55
Heart rate *(bpm)*, mean (SD)	112 (25)	106 (31)	118 (25)	0.32
Respiratory rate *(bpm)*, mean (SD)	28 (8)	30 (8)	29 (7)	0.38
Volume tidal *(mL)*, mean (SD)	1132 (231)	1078 (296)	1095 (270)	0.59
Minute ventilation *(L/min)*, mean (SD)	31 (10)	32 (9)	32 (11)	0.67
SpO2 *(%)*, mean (SD)	89 (4)	88 (3)	89 (4)	0.90
VO2 *(ml/min)*, mean (SD)	858 (318)	880 (302)	883 (318)	0.72
VCO2 *(ml/min)*, mean (SD)	787 (324)	795 (315)	805 (328)	0.86
Respiratory exchange ratio, mean (SD)	0.9 (0)	0.9 (0.1)	0.9 (0.1)	0.36
VE/VO2, median (IQR)	31 (26 to 39)	31 (27 to 39)	30 (26 to 36)	0.69
VE/VCO2, mean (SD)	37 (10)	37 (8)	36 (8)	0.83

HbO2 *(% change from baseline)*, mean (SD)	-140 (140)	-51 (67)	-31 (38)*	**0.02**
HHb *(% change from baseline)*, median (IQR)	39 (-43 to 130)	22 (7 to 228)	65 (-59 to 211)	0.96
THb *(% change from baseline)*, median (IQR)	-44 (-198 to 77)	-24 (-31 to 33)	41 (-24 to 59)	0.30
StO2 *(change from baseline, %)*, mean (SD)	-5 (3)	-3 (2)	-1 (7)	0.36
Time limit				
Dyspnoea *(BORG)*, mean (SD)	7 (2)	7 (1)	7 (2)	0.83
Lower limb fatigue *(BORG)*, mean (SD)	6 (1)	6 (1)	6 (1)	0.80
Heart rate *(bpm)*, mean (SD)	118 (26)	108 (31)	116 (26)	0.32
Systolic arterial pressure *(mmHg)*, mean (SD)	164 (27)	156 (24)	149 (29)	0.14
Diastolic arterial pressure *(mmHg)*, median (IQR)	79 (72 to 92)	78 (70 to 100)	80 (75 to 92)	0.71
Respiratory rate *(bpm)*, mean (SD)	30 (8)	31 (7)	31 (8)	0.67
Volume tidal *(mL)*, mean (SD)	1116 (302)	1067 (262)	1149 (299)	0.51
Minute ventilation *(L/min)*, mean (SD)	32 (9)	32 (8)	35 (10)*	**0.03**
SpO2 *(%)*, mean (SD)	87 (5)	88 (4)	88 (4)	0.66
VO2 *(ml/min)*, mean (SD)	899 (309)	896 (265)	970 (338)	0.09
VCO2 *(ml/min)*, mean (SD)	829 (312)	808 (271)	901 (345)**	**0.04**
Respiratory exchange ratio, mean (SD)	0.9 (0)	0.9 (0)	0.9 (0)	0.14
VE/VO2, mean (SD)	32 (7)	32 (7)	33 (9)	0.98
VE/VCO2, mean (SD)	36 (8)	36 (8)	36 (9)	0.85
HbO2 *(% change from baseline)*, mean (SD)	-109 (116)	-36 (73)	-38 (34)	0.06
HHb *(% change from baseline)*, median (IQR)	135 (-43 to 186)	24 (-32 to 477)	41 (-69 to 266)	0.62
THb *(% change from baseline)*, median (IQR)	-44 (-125 to 79)	-24 (27 to 50)	-19 (-40 to 127)	0.30
StO2 *(change from baseline, %)*, mean (SD)	-7 (6)	-2 (4)	0 (6)	0.09

Repeated measures of ANOVA or Friedman test according to the distribution.

*: Tukey's post-hoc comparison, significantly higher than sham TENS, $p<0.05$.

**: Tukey's post-hoc comparison, significantly higher than HF TENS, $p<0.05$.

[#]: Time limit of the shortest constant workload exercise testing used to define isotime for the subsequent analysis.

TENS = Transcutaneous Electrical Nerve Stimulation, VO2 = oxygen consumption, VCO2 = carbon dioxide consumption, VE ~~MV~~ = minute ventilation, HbO2 = oxyhaemoglobin and oxymyoglobin, HHb = deoxyhaemoglobin and deoxymyoblobin, THb = total haemoglobin and myoglobin, StO2 = muscle tissular oxygen saturation.