SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table I.—Literature extraction summary of seven articles identified for the systematic review. evidence grade, bias assessment. Inclusion criteria, exclusion criteria, type of study, Oxford Evidence Grades, type of intervention, type of control and measurements are given.

Study			Intervention	Control
Duarte et al. (2021)	Retrospective case series	Evidence Grade 3	Intervention: **6 patients**. Data from January 2007 to December 2016 was used. Electrical stimulation was triggered manually once every two breaths and a Phrenics Dualpex Quark® (Piracicaba, Brazil) device with the following settings: frequency of 30 hertz, pulse width of 1 ms,rise time of 0.7 ms, and current intensity of 60 mA. A dual channel unit with self-adhesive electrodes (3M®, SaintPaul, MN, USA) was used. Electrodes were attached to the left and right midaxillary line at the level of the 6th.7th,8th intercostal spaces (ICS), and to the para-xiphoid region. Inspiratory training conducted 2 x 20 min per day, 7 days a week.	Control: **6 patients**. Standard weaning protocol, intermittent oxygen-driven nebulization until successful disconnection from IMV (= ventilator-free breathing for 48 h). IMV was resumed for 12h to provide respiratory muscle rest if: respiratory rate higher than 35 breaths/min, heart rate higher than 140 beats/min, systolic blood pressure > 180 mmHg or < 90 mmHg, peripheral oxygen saturation under 90%, regardless of restlessness, sweating, altered levels of consciousness, or thoracoabdominal asynchrony.
Inclusion criteria: Tracheostomized with cervical spinal cord injury (CSCI) with tetraplegia, AIS (American Spinal Injury Association Impairment Scale) grade A injury upon admission; intact phrenic nerve function on clinical assessment, invasive mechanical ventilation (IMV) followed by prolonged weaning; TOT mask; complete medical record; CT assessment. **Exclusion criteria:** None.				
Leite et al. (2018)	Prospective Randomized Pilot Study	Evidence Grade 2	Intervention branch **Diaphragm** group (DG): **17 patients** (May to September 2014). Conventional physical therapy once a day, plus daily sessions of electrical stimulation in the diaphragm (Device: Neurodyn Multicorrentes™). Two electrodes, each placed above and below right and left sides of xiphoid process within 7th and 8th anterior intercostal space. Synchronized impulse at a frequency of 30Hz, 1s pulse increase period, 1s muscle contraction period, 1s pulse decrease period, and 20s disconnection period (session 45 min); no synchronization between contraction stimulus and breath of patients. Intervention branch **Quadriceps** group (QG): **24 patients** (May to September 2014). Conventional physical therapy once a day, plus daily sessions of electrical stimulation in quadriceps. Synchronized impulse at a frequency of 50Hz, 1s pulse increase period, 8 s muscle contraction period, 1s pulse decrease period, and 30s disconnection period. Two electrodes applied to each vastus medialis and a third to each rectus femoral. Both limbs (quadriceps) were stimulated in each procedure for 45 min.	Control: **26 patients** (January to April 2014). Control Group (CG): conventional physical therapy, which included gross motor therapy and respiratory therapy twice a day every day, including weekend, during stay in the ICU.
Inclusion criteria: Age of 18 years or more and 24 hours of MV or more. **Exclusion criteria:** Hemodynamic instability, pregnancy, BMI > 35 kg/m², neuromuscular disease at admission, brain death, peripheral vascular diseases, bone fractures, internal or external fixator, skin lesions, end-stage cancer, pacemakers, spinal injuries, inability to receive an MRC score because of the cognitive state.				
Martin et al. (2014)	Case Control Series Study	Evidence Grade 4	Intervention: **5 hemidiaphragm biopsies**. Right and left phrenic nerves alternately selected between patients for stimulation with external cardiac pacer (Medtronic 5388) with temporary cardiac pacing wire electrodes. Pacing wires sutured adjacent (~ 5 mm) to either side of phrenic nerve on stimulated side in upper thoracic space. Wires remained in the same location for entire duration of experiment. Phrenic stimulation initiated at 5 mA and increased by 3-5 mA until hemidiaphragm twitches observed. Stimulus intensity then increased to three times the threshold value, up to stimulator's maximal setting of 25 mA. Stimulation was conducted for one minute (30 pulses per minute, 1.5 msec duration). Full thickness diaphragm samples (20- 50 mg) obtained 30minutes following last stimulation bout. Determination of mitochondrial function using high-resolution respirometry of permeabilized muscle fibres. Permeabilized diaphragm muscle samples prepared for respirometry and analysed by blinded investigator. Small portions (~10-15 mg wet weight) of freshly collected muscle dissected.	Control: **5 hemidiaphragm biopsies**. Non-stimulated hemidiaphragm of same patient. Determination of mitochondrial function using high-resolution respirometry of permeabilized muscle fibres. Permeabilized diaphragm muscle samples prepared for respirometry and analysed by blinded investigator. Small portions (~10-15 mg wet weight) of freshly collected muscle dissected.
Inclusion criteria: None. **Exclusion criteria:** Prior surgery resulting in anatomical changes that would complicate obtaining muscle samples or interfere with phrenic stimulation, neuromuscular or inflammatory muscle diseases, obstructive lung disease (FEV1.0 < 60% of predicted), other lung disease, NYHA Class IV heart failure, implanted cardiac pacemaker or defibrillators, use of immunosuppressants, corticosteroids or aminoglycoside antibiotics within 60 days of surgery and serum creatinine > 1.6 mg/dl.				
Mankowski et al. (2016)	Case Control Series Study	Evidence Grade 3	Intervention: **8 hemidiaphragm biopsies**. Phrenic nerve was selected by the surgeons' convenience and stimulated with an external cardiac pacer (Medtronic 5388) with temporary cardiac pacing wire electrodes. Stimulation conducted for 1 min (30 pulses per min, 1.5 min duration) as soon as the phrenic nerve and diaphragm were exposed and every 30 min thereafter. Full thickness diaphragm samples (20–50 mg) were obtained 30 min following the last stimulation bout. Muscle biopsies from each hemidiaphragm were frozen immediately and later prepared for protein immunoblotting.	Control: **8 hemidiaphragm biopsies**. Non-stimulated hemidiaphragm of same patient. Muscle biopsies from each hemidiaphragm were frozen immediately and later prepared for protein immunoblotting.
Inclusion criteria: None. **Exclusion criteria:** Prior surgery resulting in anatomical changes that would complicate obtaining muscle samples or interfere with phrenic stimulation, neuromuscular or inflammatory muscle diseases, obstructive lung disease (FEV1.0 < 60% of predicted), other lung disease, NYHA Class IV heart failure, implanted cardiac pacemaker or defibrillators, use of immunosuppressants, corticosteroids or aminoglycoside antibiotics within 60 days of surgery and serum creatinine > 1.6 mg/dl.				
Romero et al. (2012)	Retrospective Study of non-randomized, prospectively collected data	Evidence Grade 3	Intervention: **38 patients** with phrenic nerve stimulator (PNP). Prospective collection of demographic and clinical data at first admission. Neurological examination to assess level and severity of SCI ward using ASIA impairment scale (american spinal cord injury association impairment scale). Measurement of respiratory, metabolic, cardiovascular or systemic co-morbidity using Charlson co-morbidity index. Assessment of length of stay (in days) defined as the time from first admission to hospital discharge. Assessment of length of survival defined as the time between SCI and the date of death or end of study (31st of March, 2011). Assessment of health-related quality of life (HRQL) using SF-36 questionnaire. SF-36 was filled by a psychologist in face-to-face interviews or in telephone interviews with all the surviving patients during the second half of 2010.	Control: **88 patients** with mechanical ventilation (MV). Assessment was the same as intervention group to assess differences.
Inclusion criteria: Respiratory failure due to high cervical SCI (spinal cord injury) requiring external respiratory support [either Phrenic nerve pacing (PNP) or volumetric mechanical respirator]. **Exclusion criteria:** Active pulmonary infections; cancerous disease; another underlying terminal concurrent illness.				
Dres et al. (2022)	Multicentre, open-label, randomised, controlled study	Evidence Grade 2	Intervention: **57 patients** treated with Temporary Transvenous Diaphragmatic Neurostimulation [TTDN] (from Sep. 2017 to Jan. 2020). **TTDN:** an intravenous multi-electrode stimulating catheter was inserted into left subclavian vein using Seldinger's technique. Mapping procedures before sessions ensured adequate capture of both phrenic nerves and determined stimulation thresholds. Stimulation pulses: ≤ 13.5 mA intensity, 200– 300 µs, frequencies of 4 Hz (mapping procedure) and 15 Hz (treatment). **Pacing sessions** consisted of 4 sets of 10 or 6 sets of 10 consecutive stimulations administered manually in synchrony with ventilator. Sets were separated by < 1min. 2-3 sessions (for a total of 120 stimulations) per day conducted daily for maximum 30 days, and stopped with successful SBT or extubation. If the extubation was planned before 30 days, the catheter was kept in place for 48h in case weaning was unsuccessful.	Control: **55 patients** with MV (from Sep. 2017 to Jan. 2020). Assessment was the same as intervention group to assess differences.
Inclusion criteria: > 18 years; invasive MV for > 96h; readiness-to-wean criteria and failed ≥ 2 attempts at ventilator liberation. **Exclusion criteria:** current ECMO; failed weaning due to hypervolemia; congestive heart failure; anatomy preventing left subclavian vein catheterization; congenital heart disease; neuromuscular blockade treatment; neuromuscular disease; pleural effusions (>1/3 of pleural space on chest X-ray); BMI ≥40; phrenic nerve paralysis; electrical device with potential to interfere with TTDN system; bacteraemia; hemodynamic instability; sepsis/septic shock; terminal illness with estimated life expectancy < 6 months or not committed to full care; pregnancy; lactating, participating in other study pertaining to MV weaning; vulnerable populations.			Daily weaning-readiness screening was followed by a SBT. Patients who passed the SBT were extubated (or, if tracheotomized, not reconnected to ventilator). Patients who failed SBT were put back on initial ventilator settings. Planned post-extubation non-invasive ventilation was allowed in patients with risk factors of post-extubation respiratory failure ("prophylactic non-invasive ventilation"). Unplanned non-invasive ventilation was strongly discouraged. **Measurements:** maximal inspiratory pressure (MIP), evaluation of global inspiratory muscle function performed before randomization using one-way valve, then every 72 hours, and at extubation. Diaphragmatic ultrasound performed in a subset of patients to measure diaphragm thickness and calculate the thickening fraction.
Soták et al. (2021)	Prospective, interventional, controlled, double-center study	Evidence Grade 3	Intervention: **12 patients** undergoing Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS). Two unilaterally and ten bilaterally stimulated patients: 4 predominantly ventilated on spontaneous modes (pressure support ventilation, PSV), remaining 8 patients on assist-control ventilation (ACV) or combination of ACV and PSV. **PEPNS**: Using ultrasound guidance multipolar stimulation electrode inserted near phrenic nerve in neck area. Stimulation: six stimulation treatment sessions for 2h each, occurring over 48 hours; every fourth breath was stimulated; the stimulation current adjusted to keep the patients' work of breathing (WOB) within 0.2-2 joules/L. The PEPNS system recognized onset of inspiration, regardless of ventilation mode, using an airway flow sensor which triggered the stimulation of phrenic nerves. Stimulation ceased when patient started to exhale as determined by flow sensor. Stimulation effectiveness continuously monitored by changes in tidal volume and increase in WOB.	Control: **10 patients** undergoing MV. 9 were on ACV during the enrolment period, and 1 exclusively on PSV mode.
Inclusion criteria: > 18 years, likely to be ventilated for > 48 h from recruitment. **Exclusion criteria:** LVEF < 20%, unlikely to survive 72 hours, implanted electronic device, acute myocardial infarction within 72 hours prior to screening, cardiogenic shock, bleeding diathesis, full dose systemic anticoagulation, phrenic nerve paralysis, neuromuscular muscle diseases, systemic or local infection at or around the insertion site, neutropenia, immunosuppression, pregnant or lactating, enrolled in another study, neck surgery or intervention aside from central venous line, neck cancer within the past 5 years, intra cardiac thrombus, uncontrolled hyperthyroidism and hypertension, stroke or TIA in the 6-month prior to screening, degenerative nerve disorders, elevated hemidiaphragm on chest X-ray, written informed consent not obtained.			Diaphragm thickness measured with ultrasound once a day at baseline (0 hours), after 24±4 hours, and after 48±4 hours, always at the end of expiration during relaxation of the diaphragm prior to initiation of next breath. Measured on three separate breaths with three measurements attempted on each breath when possible.