Critical Care Explorations

Original Clinical Report

Temporary Transvenous Diaphragmatic Neurostimulation in Prolonged Mechanically Ventilated Patients: A Feasibility Trial (RESCUE 1)

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Objectives: Prolonged mechanical ventilation promotes diaphragmatic atrophy and weaning difficulty. The study uses a novel device containing a transvenous phrenic nerve stimulating catheter (Lungpacer IntraVenous Electrode Catheter) to stimulate the diaphragm in ventilated patients. We set out to determine the feasibility of temporary transvenous diaphragmatic neurostimulation using this device.

Design: Multicenter, prospective open-label single group feasibility study.

Setting: ICUs of tertiary care hospitals.

Patients: Adults on mechanical ventilation for greater than or equal to 7 days that had failed two weaning trials.

Interventions: Stimulation catheter insertion and transvenous diaphragmatic neurostimulation therapy up to tid, along with standard of care.

Measurements and Main Results: Primary outcomes were successful insertion and removal of the catheter and safe application of transvenous diaphragmatic neurostimulation. Change in maximal inspiratory pressure and rapid shallow breathing index were also evaluated. Eleven patients met all entry criteria with a mean mechanical ventilation duration of 19.7 days; nine underwent successful catheter insertion. All nine had successful mapping of one or both phrenic nerves, demonstrated diaphragmatic contractions during therapy, and underwent successful catheter removal. Seven of nine met successful weaning criteria. Mean maximal inspiratory pressure increased by 105% in those successfully weaned (mean change 19.7 ± 17.9 cm H2O; p = 0.03), while mean rapid shallow breathing index improved by 44% (mean change –63.5 ± 64.4; p = 0.04).

Conclusions: The transvenous diaphragmatic neurostimulation system is a feasible and safe therapy to stimulate the phrenic nerves and induce diaphragmatic contractions. Randomized clinical trials are underway to compare it to standard-of-care therapy for mechanical ventilation weaning.

Key Words: diaphragm; lungpacer; neurostimulation; ventilator; weaning

Critically ill patients in ICUs who require mechanical ventilation (MV) commonly develop diaphragmatic dysfunction (1, 2). Diaphragmatic disuse, atrophy, and ventilator-induced diaphragmatic dysfunction (VIDD) can result from underlying medical illnesses and prolonged use of MV (2, 3). VIDD can cause difficulty weaning from MV, prolonged hospitalization, and poor functional outcomes (1, 4–6).

Although the pathophysiology is incompletely understood, several animal and human studies have demonstrated that significant diaphragmatic weakness and atrophy, both histologically and functionally, occur within hours to days after beginning MV. Furthermore, recovery of diaphragm strength is known to follow increased diaphragmatic muscle activity (7–12).

Over the last few decades, increasing numbers of patients in the United States have required MV, with approximately 30% requiring weaning from prolonged MV (13, 14). It is projected that 625,000 U.S. patients will require greater than or equal to
96 hours of MV in 2020 at costs exceeding $64 billion (15). For prolonged-wean patients, mortality increases with each additional day on MV (14). As such, there is increasing interest and research into various interventions that may attenuate the effects of VIDD and reduce the financial and human costs of prolonged MV, specifically through the use of minimally invasive diaphragmatic neurostimulation (16, 17).

Inspiratory muscle strength training (IMST), which uses sequences of breathing trials to strengthen the diaphragm and respiratory muscles, has been shown to accelerate weaning from MV in difficult-to-wean patients (18). However, there is no standardized IMST protocol and it is not an accepted standard of care. IMST trials require participation of the patient and, therefore, present challenges for use in patients who are sedated or critically ill. Surgically implanted diaphragmatic and phrenic nerve stimulators have been used since the 1970s to contract the diaphragm rhythmically; however, use of this surgical intervention is intended for long-term use and is often not feasible or appropriate for critical care patients (19). Finally, magnetic stimulation has been cumbersome and not applicable in a standard ICU setting (20).

The study uses a novel, Food and Drug Administration (FDA)-designated breakthrough device utilizing a phrenic nerve stimulation catheter, the Lungpacer IntraVenous Electrode Catheter (Lungpacer Medical USA Inc., Exton, PA), to capture the phrenic nerve and stimulate the diaphragm in patients unable to wean from MV. The goal of temporary transvenous diaphragmatic neurostimulation (TTDN) is to recondition and strengthen the diaphragm, thereby facilitating weaning from MV in patients with respiratory pump dysfunction and prolonged MV dependency. It is, in many respects, “physical therapy for the diaphragm.” Animal studies that used the system have shown that the use of transvenous phrenic nerve stimulation mitigates VIDD (21), and the first-in-human clinical trials with the system safely produced diaphragmatic contractions that were synchronized with MV (22).

In this study, we assessed the feasibility and safety of insertion and removal of the stimulation catheter and the ability to achieve diaphragmatic contractions via phrenic nerve stimulation in patients with prolonged MV dependency.

**MATERIALS AND METHODS**

**Study Design**

RESCUE 1 was a multicenter, prospective open-label single treatment group feasibility study of adult patients in the United States who were dependent on MV for at least 7 days and had failed at least two weaning trials. Patients were to receive the TTDN in addition to standard of care.

**Study Device**

A novel, temporary, percutaneously placed device intended to electrically stimulate the phrenic nerves using the transvenous indwelling central venous multi-electrode stimulation catheter to induce diaphragmatic contraction in conjunction with MV.

The stimulation catheter is a 9.5F, single-use, central venous catheter with two embedded electrode arrays (proximal and distal) that is placed in the left subclavian vein. The proximal and distal electrode arrays stimulate the left and right phrenic nerves, respectively. The catheter also has a single lumen for IV fluid or medication administration. The catheter is attached to an external pulse generator control unit which, when manually activated, delivers electrical impulses through the catheter electrodes (Fig. 1). Temporary TTDN is modeled on classic muscle rehabilitation therapy, which initially consists of exercise at a low intensity that then progresses to higher intensities over time as the muscle develops. In the same way, each study subject was advanced through the progressive diaphragm muscle training regime at his or her own rate based on individual tolerance and diaphragm muscle performance. As such, patients received up to three TTDN sessions per day. Each session consisted of a maximum of four sets of ten diaphragmatic stimulations. There were no fewer than 3 hours between daily sessions. Patients’ comfort levels were assessed during and after diaphragmatic stimulation.

Prior to each TTDN session, the mapping process was performed to identify the most suitable electrode combination that resulted in contraction of the diaphragm at the lowest stimulation intensity, which was used as the patient’s baseline threshold intensity. The maximum stimulation intensity for each session was identified by...
the delivery of a small number of single stimulations (approximately 4–10), starting at the baseline threshold intensity and increasing in small increments until diaphragmatic contractions were detected by the device operator.

During the mapping process, diaphragm contractions were assessed by palpating the patient’s upper abdomen over the hemidiaphragm that was being stimulated. During phrenic nerve stimulation, investigators could detect diaphragm movement, which is accompanied by increased tidal volumes (Vt) as compared with unstimulated spontaneous breaths or breaths triggered by the ventilator. The mapping process was repeated prior to each treatment session. Although secured externally, the stimulation catheter may change position within the vein, thereby altering the position of the electrodes on the catheter relative to the phrenic nerves. Such movement may be due to changes in the patient’s position or fluid status from one therapy session to the next.

**Outcomes**
The primary outcomes were the feasibility and safety of the stimulation catheter insertion, successful electrode mapping, electrophrenic stimulation with diaphragm contraction, and safe removal in patients who received continuous MV. Secondary outcomes included the assessment of the proportion of patients weaned, change from baseline in the rapid shallow breathing index (RSBI), and change from baseline in maximal inspiratory pressure (MIP) which was an indirect measure of diaphragmatic strength. Successful weaning was defined as passing the protocol-specific ventilator liberation trial (VLT) and liberation from MV for 48 hours. Adverse events were collected throughout the study. Discomfort was measured at the start of the therapy and at the conclusion using the neurostimulation and discomfort tool which included the Wong-Baker faces pain rating scale (23).

**Rapid Shallow Breathing Index and Maximal Inspiratory Pressure**
RSBI and MIP were measured at the time of study enrollment, every 7 days during the study, and prior to extubation or at day 30 if the subject was not able to be extubated.

The RSBI, defined as the ratio of respiratory frequency (f) to Vr in liters, was measured at the initiation of each daily protocol-specific VLT and served as a daily assessment of readiness to wean. Patients who are not able to breathe independently will usually take frequent, shallow breaths. Because the RSBI reflects the ratio of f/Vr, patients who are unable to breathe independently will likely demonstrate higher-than-normal scores on the RSBI. The RSBI was evaluated for 60 seconds on pressure support of 0 cm H2O and positive end-expiratory pressure (PEEP) of 0 cm H2O.

The Richmond Agitation-Sedation Scale (RASS) score was documented prior to assessing the MIP. Patients had to be able to respond to one-step commands in order to perform MIP measurements. The MIP was measured using an electronic pressure recording manometer connected to the subject’s endotracheal tube or tracheostomy with a one-way valve. All investigators were trained on a standardized method of performing the MIP measurement (24). Patients were suctioned if needed before MIP measurement and placed on 100% oxygen for 2 minutes before each measurement. Unless clinically contraindicated, the head of the bed was elevated to 30°. During each MIP recording, the maximal (most negative) reading out of three attempts was recorded.

**Ventilator Liberation Trial**
Prior to enrollment, each patient failed two or more documented attempts to wean from MV on separate calendar days, one of which was the required protocol-specific VLT. The protocol-specific VLT was conducted on pressure support of 0 cm H2O and PEEP of 0 cm H2O. After enrollment in the study, daily protocol-specific VLTs were conducted at least 2 hours before the first TTDN session of the day. A subject was considered to have passed a protocol-specific VLT if they were able to tolerate it for at least 30–120 minutes if endotracheally intubated or for 24 hours if they had a tracheostomy tube. After passing the protocol-specific VLT, the patient entered a 48-hour window and if they did not require reintubation or resumption of MV they were considered successfully weaned and the stimulation catheter was removed.

**Ethics**
The study was carried out according to Good Clinical Practice guidelines and under the guiding principles detailed in the Declaration of Helsinki and all applicable local laws and regulations. The study protocol was approved by the FDA under an investigational device exemption, and all participating centers received approval from the appropriate Institutional Review Boards (IRBs) before the start of the study: University of Florida (W-IRB 20183095), UT Southwestern (UT-IRB STU032017-018), and Temple University (W-IRB 20170722).

**Study Population**
Adult patients 18 years and older who were receiving continuous MV for at least 7 days were approached for potential inclusion in this study. All patients, or their legally authorized representative, provided written informed consent for participation prior to initiation of any study-related procedures. Consented patients were medically stable and considered ready to be weaned from MV by their medical providers; however, all had failed at least two VLTs.

Patients were excluded if they were hypervolemic at the time of study enrollment based on the treating physician’s discretion, had an implanted electrical device, were diagnosed with a known neuromuscular disorder upon ICU admission, had suspected or known phrenic nerve paralysis, had an effusion that occupied more than one-third of the pleural space on either side, were hemodynamically unstable, had bacteremia within 48 hours of assessment of study inclusion, were receiving extracorporeal membrane oxygenation, were prescribed neuromuscular blockers, had a body mass index greater than or equal to 40, were known or suspected to be pregnant, were terminally ill with a life expectancy of fewer than 6 months, or had a known congenital heart condition or abnormal vasculature anatomy that would prevent or complicate insertion of the catheter.

**Statistical Analysis**
Means, sds, and ranges are reported for continuous variables and the number and percent of observations for categorical variables.
Paired comparisons between baseline and the last available measure, for all variables, were made using the paired $t$ test as appropriate. SAS v9.4 (SAS Institute, Cary NC) was used for all analyses.

RESULTS

Patient Population

Between June 2017 and January 2018, 14 patients were conditionally enrolled in the study. Three were screen failures because they passed the protocol-specific VLT after conditional enrollment. A total of 11 patients were successfully enrolled across three study sites. Two patients were subsequently discontinued from the study due to an inability to fully advance the commercial guidewire, which prevented the stimulation catheter placement. Nine patients underwent successful catheter placement, of which seven completed the study (77.8%) with a day 30 follow-up assessment (Consolidated Standards of Reporting Trials diagram presented in Fig. 2). The other two patients exited the study early; one was newly diagnosed with amyotrophic lateral sclerosis (ALS) after enrollment in the trial, and the other was transferred to a long-term care facility. The patient who was newly diagnosed with ALS died following a request to withdraw life support. The patient who transferred to a long-term care facility was followed after their transfer and was weaned prior to study day 30. Weaning outcomes for these two patients were obtained to day 30 and are included in the analysis.

Among the 11 enrolled patients, the mean age was 62.4 ± 10.2 years and the mean time on MV prior to enrollment was 19.7 ± 17.9 days, with approximately half of the patients (6/11, 54.5%) having a tracheostomy placed prior to enrollment. The characteristics of these patients are described in Table 1.

Stimulation Catheter Placement and Therapy

Nine patients underwent ultrasound or landmark-guided catheter placement via the left subclavian vein, had their left and/or right phrenic nerves successfully mapped, demonstrated consistent diaphragm contraction via phrenic nerve neurostimulation, and underwent successful removal at the end of the study period. Seven of the nine patients (77.8%) met criteria for successful weaning by day 30. One patient’s data were not included in the number of MV days to weaning since the exact day of weaning was unknown after transfer to a long-term acute care weaning facility. Among those who were successfully weaned, the mean time on MV after catheter placement was 16.7 ± 5.4 days. Two patients underwent tracheostomy after enrollment in the study. Two patients required non-invasive ventilation postextubation.
None of the successfully weaned patients required placement back on the ventilator after 48 hours.

Patients were awake during the therapy sessions and minimally sedated as determined by the RASS score. Perceived discomfort was measured at the start of the therapy and at the conclusion using the neurostimulation and discomfort tool which included the Wong-Baker faces pain rating scale (23). No adverse events were associated with catheter placement or removal. A treatment-related adverse event involved mobilization of mucus plugs after initiation of therapy in a patient with bibasilar atelectasis. This event required bronchoscopy to achieve airway clearance, and the patient was later successfully weaned from MV. No other treatment-related adverse events were reported. Pain and discomfort were measured at the start of the therapy and at the conclusion, and none of the patients experienced pain. Most patients compared TTDN therapy to hiccups or a pulling and tugging sensation.

Changes in Respiratory Function and Muscle Strength
In the nine patients who underwent TTDN, MIP improved by 64%, with a mean change in MIP of 13.9 ± 20.6 cm H₂O (p = 0.08). Among those who were successfully weaned (n = 7), MIP improved by 105%, with a mean change in MIP of 19.7 ± 17.9 cm H₂O (p = 0.02) (Fig. 3). RSBI improved by 44% with a mean change of –62.7 ± 60.4 (p = 0.01) among all enrolled patients and –63.5 ± 64.4 (p = 0.04) among successfully weaned patients (Fig. 4).

DISCUSSION
We report the results of an early phase safety and feasibility trial of a novel, FDA-designated breakthrough device delivering temporary TTDN in a small cohort of patients suffering from failure to wean from MV. All patients were considered to have VIDD at the time of study enrollment. One was subsequently found to have ALS, highlighting the challenge of accurately identifying the presence of VIDD.

It is estimated that approximately 30% of ventilated ICU patients may require prolonged weaning from a ventilator (14). Failure to wean from MV carries high morbidity and mortality and has been associated with poor long-term outcomes (1, 4–6, 25). The VIDD and atrophy that occurs in this population is one of the leading causes of prolonged ventilator weaning and impacts patient clinical outcomes (6).

In humans, even brief periods of MV can lead to diaphragm atrophy and loss of muscle strength (9, 11, 25). Most patients with difficult weaning exhibit a high respiratory drive, and it is thought that diaphragm weakness causes this high level of respiratory drive. The high respiratory drive in difficult-to-weep patients typically manifests itself as a rapid but shallow breathing pattern. If the problem is a weak diaphragm, strengthening the diaphragm is an obvious potential solution. It is widely accepted in physical training and rehabilitation that in order to improve muscle strength, muscles must produce high-force contractions, and only a small number of high-intensity contractions are needed. The rapid rate, shallow breathing pattern seen in weaning patients during periods of reduced MV support or even completely unsupported breathing trials is a low muscle force, high number of contractions (hundreds or even thousands of contractions) motor program as opposed to a small number (dozens) of high-force muscle contractions needed to improve strength. This technique allows therapists to induce a small number of high-force, maximal motor neuron stimulations to the hemidiaphragm, thus increasing diaphragm strength.

Different forms of IMST have emerged over the last several years to address this problem; however, no formal multicenter randomized clinical trials have been conducted (24). The IMST method described by Martin et al (24) can induce improvements in respiratory muscle strength and weaning outcomes but requires that the patients tolerate repeated periods of being disconnected from the ventilator circuit and are sufficiently alert to comply with training instructions. Additionally, the force of the inspiratory efforts is controlled by the patients with the manual IMST technique. It is difficult for therapists to assess the patient’s degree

![Figure 3. Change in maximal inspiratory pressure (MIP) in enrolled patients with stimulation catheter placed and in those who were successfully weaned. The open circle represents the mean. LIVE = Lungpacer IntraVenous Electrode.](image)

![Figure 4. Change in rapid shallow breathing index (RSBI) scores in enrolled patients with stimulation catheter placed and in those successfully weaned. The open circle represents the mean. LIVE = Lungpacer IntraVenous Electrode.](image)
of cooperation with IMST efforts without invasive measures or a data acquisition system to measure inspiratory flow, pressure, and Vt during inspiratory efforts.

Temporary TTDN has several advantages. First, the patient does not have to be fully alert to undero therapy, and sedated patients can undergo training. Electrical neurostimulation of the diaphragm can maintain, and may even improve, function versus inactive tissue. Indeed, a series of studies have shown that intermittent electrical stimulation of the human hemidiaphragm during prolonged cardiac surgery can maintain or improve muscle function versus the inactive hemidiaphragm (16, 17). These researchers have shown that intermittent stimulation (30 stimulations over 1 min, every 30 or 60 min) of one hemidiaphragm during a 5–6 hour surgery can reduce markers of oxidative stress in the intermittently active hemidiaphragm versus an inactive hemidiaphragm (17). With this experimental paradigm, mitochondrial respiration was also improved in the intermittently active hemidiaphragm versus the inactive hemidiaphragm (16).

Most importantly, single muscle fiber contractile force was higher in stimulated human hemidiaphragm fibers versus the inactive hemidiaphragm fibers (26).

Although placing a central venous catheter is not a trivial matter and does entail some risk, the risks of prolonged dependence on MV are significant (27, 28). Prolonged dependence on MV impedes mobilization and rehabilitation in the best of ICUs. More importantly, dependence on MV for more than 14–28 days incurs a significant risk of mortality (29). Inspiratory muscle weakness has been shown to be an independent contributor to mortality in patients who require MV (2, 28). Currently, there are no accepted pharmacological or muscle rehabilitation treatments for ventilator-induced diaphragm weakness, a major contributor to weaning difficulty.

Current methods of IMST can significantly improve MIP by 7 cm H2O and the RSBI by 15 breaths/min/L, while facilitating weaning from MV and possibly reducing ICU and hospital length of stay (30). IMST methods induce a forceful global inspiratory effort which requires increased force generation within the diaphragm and accessory muscles of respiration (24). In contrast, TTDN is specific to the diaphragm via phrenic nerve neurostimulation and is not believed to directly induce contractions in accessory muscles. Regardless of the effects of TTDN on both the accessory respiratory muscles and the diaphragm, the improvement in MIP in this study with TTDN was slightly higher than in the IMST study reported by Martin et al (24). Additionally, TTDN also improved RSBI. The number of subjects studied thus far is too small to make a valid statistical contrast, but in this safety and feasibility study, these data support the hypothesis that TTDN can induce similar improvements in respiratory function to the global, manual IMST method (24, 30).

One patient experienced a treatment-related adverse event associated with the use of the TTDN. This patient experienced acute desaturation after initiating a daily session of TTDN, requiring bedside fiberoptic bronchoscopy to suction out a large mucus plug from their endotracheal tube. It appears that the diaphragmatic contractions during TTDN expanded atelectatic sections in the lung bases and mobilized mucus plugs from the lung bases.

This study has a number of strengths. Seven of nine patients who received TTDN were successfully weaned from MV after 8–22 days of diaphragm pacing. TTDN appears to be a feasible and safe means of diaphragm pacing in patients with difficulty weaning from MV and also demonstrates the potential for therapeutic efficacy. This will be tested in two prospective randomized efficacy trials that are currently underway (31). TTDN effectively strengthened the diaphragm, as shown by improved inspiratory muscle strength and respiratory function, in patients who required prolonged MV and who previously failed at least two weaning attempts. The improvement in the MIP and RSBI in this study exceeded the average improvements seen with current methods of IMST (30).

This study also has several limitations. A small number of patients were enrolled in the trial. Investigators were unable to place the guidewire (precluding catheter placement) in two patients. Although it is unclear why the commercial guidewire could not be advanced in these patients, anatomical barriers are a potential cause. Not all patients have an accessible left subclavian vein. Future studies may address this issue with the use of fluoroscopy in patients with difficult line placement or potential catheter placement via a left jugular approach (32).

CONCLUSIONS

The results of the RESCUE 1 study suggest that TTDN is safe and feasible in patients with difficulty weaning from prolonged MV. This novel therapy approach requires further evaluation in a larger population and is presently the subject of two multicenter, prospective randomized controlled clinical trials.

Dr. Ataya takes responsibility for the content of the article, including data and analysis. All authors participated in undertaking conception, design, and writing of the article. All authors have read, improved, and approved the final article.

Lungpacer Medical is the study sponsor at each site where the study was conducted.

The authors have disclosed that they do not have any potential conflicts of interest.

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REFERENCES

1. Demoule A, Jung B, Prodanovic H, et al: Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact—a prospective study. Am J Respir Crit Care Med 2013; 188:213–219
2. Supinski GS, Callahan LA: Diaphragm weakness in mechanically ventilated critically ill patients. Crit Care 2013; 17:R120
3. Laghi F, Cattapan SE, Jaburan A, et al: Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 2003; 167:120–127
4. Dasta JF, McLaughlin TP, Mody SH, et al: Daily cost of an intensive care unit day: The contribution of mechanical ventilation. Crit Care Med 2005; 33:1266–1271
5. Jung B, Moury PH, Mahul M, et al: Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med 2016; 42:853–861
6. Goligher EC, Dres M, Fan E, et al: Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. *Am J Respir Crit Care Med* 2018; 197:204–213

7. Vassilakopoulos T, Petrof BJ: Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med* 2004; 169:336–341

8. Bruells CS, Bergs I, Rossaint R, et al: Recovery of diaphragm function following mechanical ventilation in a rodent model. *PLoS One* 2014; 9:e87460

9. Welvaart WN, Paul MA, Stienen GJ, et al: Selective diaphragm muscle weakness after contractile inactivity during thoracic surgery. *Ann Surg* 2011; 254:1044–1049

10. Hussain SN, Cornachione AS, Guichon C, et al: Prolonged controlled mechanical ventilation in humans triggers myofibrillar contractile dysfunction and myofilament protein loss in the diaphragm. *Thorax* 2016; 71:436–445

11. Levine S, Nguyen T, Taylor N, et al: Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008; 358:1327–1335

12. Powers SK, Wiggs MP, Sollanek KJ, et al: Ventilator-induced diaphragm dysfunction: Cause and effect. *Am J Physiol Regul Integr Comp Physiol* 2013; 305:R464–R477

13. Wünsch H, Linde-Zwirble WT, Angus DC, et al: The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010; 38:1947–1953

14. Béduneau G, Pham T, Schortgen F, et al; WIND (Weaning according to a New Definition) Study Group and the REV A (Réseau Européen de Recherche en Ventilation Artificielle) Network‡: Epidemiology of weaning prolonged controlled ventilation in humans feasibility. *Crit Care Med* 2017; 195:772–783

15. Zilberberg MD, de Wit M, Shorr AF: Accuracy of previous estimates for the phrenic nerves for diaphragm conditioning: A normative study of feasibility and optimal settings. *Appl Physiol Nutr Metab* 2011; 36:1001–1008

16. Martin AD, Joseph AM, Beaver TM, et al: Effect of intermittent phrenic nerve stimulation during cardiothoracic surgery on mitochondrial respiration in the human diaphragm. *Crit Care Med* 2014; 42:e152–e156

17. Mankowski RT, Ahmed S, Beaver T, et al: Intraoperative hemidiaphragm electrical stimulation reduces oxidative stress and upregulates autophagy in surgery patients undergoing mechanical ventilation: Exploratory study. *J Transl Med* 2016; 14:305

18. Smith BK, Gabrielli A, Davenport PW, et al: Effect of training on inspiratory load compensation in weaned and unweaned mechanically ventilated ICU patients. *Respir Care* 2014; 59:22–31

19. Onders RP, Elmo M, Kaplan C, et al: Long-term experience with diaphragm pacing for traumatic spinal cord injury: Early implantation should be considered. *Surgery* 2018; 164:705–711

20. Adler D, Gottfried SB, Bautin N, et al: Repetitive magnetic stimulation of the phrenic nerves for diaphragm conditioning: A normative study of feasibility and optimal settings. *Crit Care Med* 2017; 195:339–348

21. Reynolds SC, Meyyappan R, Thakkar V, et al: Mitigation of ventilator-induced diaphragm atrophy by transvenous phrenic nerve stimulation. *Am J Respir Crit Care Med* 2017; 195:889–895

22. Reynolds S, Ebner A, Meffen T, et al: Diaphragm activation in ventilated patients using a novel phrenic nerve temporary pacing catheter: First-in-humans feasibility. *Am J Respir Crit Care Med.* 2016;193:A7655

23. Wong-Baker FACES Foundation: Wong-Baker FACES® Pain Rating Scale. 2016. Available at: http://www.WongBakerFACES.org. Accessed February 12, 2020

24. Martin AD, Smith BK, Davenport PD, et al: Inspiratory muscle strength training improves weaning outcome in failure to wean patients: A randomized trial. *Crit Care* 2011; 15:R84

25. Jaber S, Petrof BJ, Jung B, et al: Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med* 2011; 183:364–371

26. Ahn B, Beaver T, Martin T, et al: Phrenic nerve stimulation increases human diaphragm fiber force after cardiothoracic surgery. *Am J Respir Crit Care Med* 2014; 190:837–839

27. Bigatello LM, Steffox HT, Berra L, et al: Outcome of patients undergoing prolonged mechanical ventilation after critical illness. *Crit Care Med* 2007; 35:2491–2497

28. Damuth E, Mitchell JA, Bartock JL, et al: Long-term survival of critically ill patients treated with prolonged mechanical ventilation: A systematic review and meta-analysis. *Lancet Respir Med* 2015; 3:544–553

29. Medrinal C, Prieur G, Frenoy É, et al: Respiratory weakness after mechanical ventilation is associated with one-year mortality - a prospective study. *Crit Care* 2016; 20:231

30. Elkins M, Dentice R: Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: A systematic review. *J Physiother* 2015; 61:125–134

31. Evans D, Shure D, Clark L, et al: Temporary transvenous diaphragm pacing vs. standard of care for weaning from mechanical ventilation: Study protocol for a randomized trial. *Trials* 2019; 20:60

32. Gaini M, Bassi TG, Clark L, et al: Transvascular stimulation of left and right phrenic nerves using a single catheter via jugular access - a feasibility study. *A J Respir Crit Care Med* 2019; 199:A2755