Initial Assessment of the Percutaneous Electrical Phrenic Nerve Stimulation System in Patients on Mechanical Ventilation

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Objectives: Maintaining diaphragm work using electrical stimulation during mechanical ventilation has been proposed to attenuate ventilator-induced diaphragm dysfunction. This study assessed the safety and feasibility of temporary percutaneous electrical phrenic nerve stimulation on user-specified inspiratory breaths while on mechanical ventilation.

Design: Two-center, nonblinded, nonrandomized study.

Setting: Hospital ICU.

Patients: Twelve patients mechanically ventilated from 48 hours to an expected 7 days.

Interventions: Leads were inserted to lie close to the phrenic nerve in the neck region using ultrasound guidance. Two initial patients had left-sided placement only with remaining patients undergoing bilateral lead placement. Percutaneous electrical phrenic nerve stimulation was used for six 2-hour sessions at 8-hour intervals over 48 hours.

Measurements and Main Results: Data collected included lead deployment success, nerve conduction, ventilation variables, work of breathing, electrical stimulation variables, stimulation breath synchrony, and diaphragm thickness measured by ultrasound at baseline, 24, and 48 hours. Primary endpoints included ability to capture the left and/or right phrenic nerves and maintenance of work of breathing within defined limits for 80% of stimulated breaths. Lead insertion was successful in 21 of 22 attempts (95.5%). Analysis of 36,059 stimulated breaths from 10 patients with attempted bilateral lead placement demonstrated a mean inspiratory lag for phrenic nerve stimulation of 23.7 ms ($p < 0.001$ vs null hypothesis of <88ms). Work of breathing was maintained between 0.2 and 2.0 joules/L 96.8% of the time, exceeding the 80% target. Mean diaphragm thickness increased from baseline by 7.8% at 24 hours ($p = 0.022$) and 15.0% at 48 hours ($p = 0.0001$) for patients receiving bilateral stimulation after excluding one patient with pleural effusion. No serious device/procedure-related adverse events were reported.

Conclusions: The present study demonstrated the ability to safely and successfully place percutaneous electrical phrenic nerve stimulation leads in patients on mechanical ventilation and the feasibility of using this approach to synchronize electrical stimulation with inspiration while maintaining work of breathing within defined limits. (*Crit Care Med* 2020; 48:e362–e370)

Key Words: diaphragm atrophy; mechanical ventilation; phrenic nerve; ventilator-induced diaphragm dysfunction; ventilator weaning

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Mechanical ventilation is one of the most common interventions for patients admitted to ICUs with up to 40% of patients requiring this means of ventilatory support (1). The number of patients requiring prolonged acute mechanical ventilation is increasing and is expected to exceed 1 million patients in 2020 in the United States at a cost of more than $64 billion (2). The time required to wean patients from mechanical ventilation is proportional to ICU length of stay with 45% of ICU patients experiencing difficult or prolonged weaning (3). Extended time on ventilatory support also increases patient morbidity, mortality, and healthcare costs (4).

The development of ventilator-induced diaphragm dysfunction (VIDD) is a significant barrier to the successful weaning of patients from ventilators and contributes to prolonging weaning times (5, 6). Diaphragmatic weakness and atrophy develop rapidly in patients started on mechanical ventilation with significant correlation to duration of ventilatory support (5).

A recent study has reported that 60–80% of mechanically ventilated patients manifest clinically significant diaphragm dysfunction (7). Diaphragmatic weakness, which occurs in as little as 18 hours, has been shown to be due to respiratory muscle contractile dysfunction resulting from proteolysis (8). Diaphragm thickness, as measured by ultrasound, has also been shown to decline within 3–4 days, with diaphragm atrophy associated with the length of mechanical ventilation (9). Strategies that aim to maintain diaphragm work during mechanical ventilation have been shown to attenuate this decrease in diaphragm strength (10, 11).

Stimulation of the phrenic nerves to induce diaphragmatic movement in a patient with respiratory paralysis was first reported by Sarnoff in 1948 (12). Subsequently, the use of implantable diaphragmatic pacemakers has been clinical validated for patients with spinal cord injuries and central hypoventilation syndrome (13). Intermittent electrical stimulation of the phrenic nerves to pace the diaphragm has been hypothesized as a strategy to minimize the reduction in diaphragm atrophy and strength over time, possibly leading to reduced weaning times in patients on mechanical ventilation (5). In line with the above, the use of a temporary, percutaneous, transvenous phrenic nerve pacing catheter to prevent diaphragm atrophy and ventilator pressure has recently been explored (14).

The phrenic nerve originates from the anterior rami of C3 through C5 and traverses the neck, heart, and lungs to reach the diaphragm. The relatively superficial nature of the phrenic nerve within the cervical region together with ultrasonic visualization enables the least invasive access point to insert percutaneous stimulation leads with local anaesthesia. The present study was designed to assess the ability to insert disposable multipolar leads (pdSTIM L4300 Leads, Stimdia Medical, Edina, MN) in the neck region at the patient beside using ultrasound guidance to facilitate temporarily stimulation of the phrenic nerve. The study also explored the ability to control inspiratory work of breathing (WOB) within known safe electrical stimulation variables in synchrony with mechanical ventilation. Prior to initiating human studies, the study sponsor (Stimdia Medical) conducted multiple preclinical animal studies under Device Design Control and Good Laboratory Practices using canine, caprine, and porcine models to evaluate the mitigating effect of phrenic nerve pacing on VIDD and to assess potential lead insertion techniques to ensure there was no damage to the surrounding tissue or nerves. This testing also demonstrated that diaphragm strength was maintained in paced versus non-paced animals. Data from these studies (unpublished) was included as a part of the study applications submitted to and approved by the Irish Health Products Regulatory Authority (HPRA) and the Czech Institute for Drug Control (SÚKL) prior to initiation of the study.

METHODS

Study Design
This was a two-center, single-arm feasibility study to evaluate the safety and performance of the PEPNS System in hospitalized ICU patients requiring mechanical ventilation. All study documentation was reviewed and approved by the appropriate Czech SÚKL and Irish HPRA regulatory bodies, including the Military University Hospital Prague and Beaumont Hospital ethics committees, prior to subject screening and enrollment. The study was registered with ClinicalTrials. gov (NCT03559933).

Primary endpoints (**Table 1**) were the ability of the system to mobilize the diaphragm within normal WOB levels. Secondary endpoints (Table 1) included the percentage of patients who had successful lead placement, the ability to synchronize electrical stimulation with inspiration to mobilize the diaphragm, and the percentage of patients who experienced serious device/procedure-related adverse events during the study. Diaphragm thickness, measured by ultrasound at baseline, 24, and 48 hours, and time to weaning from ventilatory support were also recorded.

Patients
Inclusion criteria required adult patients being able to give written informed consent or relative assent and be likely to be ventilated in the opinion of the admitting physician for greater than 48 hours. Exclusion criteria included unlikely to survive 72 hours, having an implanted pulse generator, undergone neck surgery, having a degenerative nerve disorder or elevated hemidiaphragm, etc. Inclusion/exclusion criteria are detailed in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/F345). The first two subjects enrolled had a single lead placed next to the left phrenic nerve only, with a neurologic assessment (nerve conduction latency and compound motor action potential amplitude) prior to lead insertion and once again at the 30-day follow-up examining for potential nerve injury due to the lead insertion or electrical stimulation. Following successful determination of device safety by a neurophysiologist, leads were placed bilaterally in the remaining patients enrolled in the study.

Lead Placement
After screening for inclusion/exclusion criteria and obtaining a written informed consent or relative assent, patients underwent ultrasound assessment of the neck to ensure the ability to visualize and locate anatomical landmarks for optimal lead placement. Ultrasound visualization was performed with a bedside system (SonoSite, Bothell, WA, or equivalent) using nerve mode with a 13-6 MHz range probe.

The percutaneous leads were placed using a through the needle approach within the fascial plane dividing the sternocleidomastoid superficially and the anterior scalene muscles deep using ultrasound imaging to aid needle guidance (**Fig. 1**). The flexible electrode leads were 0.87 mm in diameter with the electrode charge density limited to 25 μC/cm^2 per phase. The leads were connected to a customized percutaneous electrical phrenic nerve stimulation (PEPNS) console which delivered stimulation breaths at user-specified breath count intervals during inspiration while measuring the WOB in joules/liter (J/L) (Fig. 1). The PEPNS console and pdSTIM leads were available under investigational use only.

TABLE 1. Endpoint Results

Primary Endpoints
1. Capture of the left and/or right phrenic nerve > 80% with an output variables of <10.5 volts
• Data from 36,059 stimulated breaths for the 10 patients with bilateral lead placement (excluding the initial two patients with left-sided lead placement only) was assessed to determine if the primary endpoints were achieved.
• A linear regression demonstrated a capture rate of 96.6%, with a one-sided lower 98.8% confidence bound of 93.2% with no patient requiring stimulation voltages above the 10.5-volt threshold.
Since the lower confidence bound is <80% goal, the null hypothesis is rejected and the primary endpoint is considered met.
2. WOB kept between 0.2 and 2 joules/L for 80% of stimulated breaths.
• WOB was maintained between 0.2 J/L and 2.0 J/L for 96.8% (95% CI: 96.6–97.0%) of samples.
• Since the lower bound of this CI exceeded the 80% target, this primary endpoint was also considered met.
Secondary Endpoints
1. Percentage of patients who had safe and successful placement of the multipolar leads in the left and right phrenic nerve utilizing ultrasound guidance.
• Lead insertion was successful in 21 of 22 attempts (95.5%) for the entire study population and in 19 of 20 attempts (95.0%) for the 10 patients with bilateral lead placement.
• Right side lead placement was unsuccessful for one patient due to a prominent suprascapular artery or transverse cervical artery resulting in the inability to properly place the lead and obtain desired electrical stimulation.
2. Phrenic nerve stimulation in synchrony with MV breaths to verify that it occurs with inspiration.
• Synchronization of electrical stimulation with inspiration was determined at the beginning of inspiration and expiration.
• Data were compared with a detection time of 88 ms which is considered fast for inspiratory breath detection (18).
• Mean inspiratory lag was analyzed for 36,055 of the 36,059 stimulated breaths due to four breaths being excluded since the algorithm did not detect the inspiratory trigger and a lag could not be calculated.
• Analysis of phrenic nerve stimulation in synchrony with MV breaths yielded a mean inspiratory lag of 23.66 ms (95% CI: 23.52–23.80).
• With the null hypothesis defined as the mean Lag >88ms ($p < 0.0001$), the null hypothesis is rejected, and this secondary endpoint was considered met.
3. Percentage of patients who experience one or more serious device/procedure-related adverse events.
• No serious device/procedure related adverse events reported during the study.
• The four patient deaths were determined to be not device or procedure related by the principle investigators and adjudicated as such by the independent Clinical Events Committee.
• The death incidence of 33% in this study (4/12) was within what has been reported in the literature of 34.5% for mechanically ventilated patients in hospital ICU and 45.7% for patients in the medical ICU with neurologic complications (19).

MV = mechanical ventilation, WOB = work of breathing.

The leads were placed using separate echogenic, 18 G × 75 mm Tuohy tipped needle using ultrasound for visual guidance. Figure 1 shows the ideal lead placement approach across the phrenic nerve based on the manufacturer's recommendation. The needle position was clearly visible with ultrasound as it traversed the fascial plane deep to the sternocleidomastoid muscle (SCM) and superficial to the anterior scalene muscle (ASM). A saline primed needle was advanced under ultrasound guidance through a 1 mm skin incision until the tip was at the base of the neck in close apposition to the internal jugular vein and carotid artery. Hydrodissection was used to expand the tissue plane between the ASM and SCM, the expected location of the phrenic nerve. When the needle was in position, the lead was inserted to the tip of the needle and the needle withdrawn under ultrasound guidance leaving the lead in the needle's place. The lead was connected to the PEPNS console to achieve capture of the phrenic nerve. Stimulation voltages and currents ranged between 0.5 and 10.5 volts and 0.5 and 12 mA.

Electrical stimulation was delivered in synchrony with ventilator inspiration based upon defined inspiratory and expiratory trigger flow limits. Each patient was stimulated for six separate 2-hour sessions over a 48-hour treatment period with leads being disconnected between stimulation sessions. Leads were removed at the end of the 48-hour treatment period.

Measurements
Supplemental Table 2 (Supplemental Digital Content 1, http://links.lww.com/CCM/F345) outlines demographic and study

TABLE 2. Patient Demographics

Patient ID[a]	Mode(s) of Ventilation (Humidification)	Screening Blood Pressure (mm Hg)	Days on Ventilation Before First Stimulation	Age (yr)	Body Mass Index and (Weight in kg)	Neck Circumference at Cricoid Cartilage (cm)	Cause of Admission
P01S02	PS/CPAP, (HH)	152/68 (96)	3.7	70	21.3 (60)	41	COPD, TBI, alcoholism
P02S02	PS, (HH)	151/83 (109)	6.8	56	34.2 (100)	47	TBI
P03S01[b]	BIPAP, SIMV-ASB, (HME)	155/60 (91.7)	5.7	74	26.2 (85)	42	Rupture of arterio-venous malformation
P04S01	BIPAP, CPAP, SIMV-ASB, CPAP-ASB, SIMV-ASB, (HME)	120/50 (73.3)	5.5	58	29.4 (90)	44	TBI, respiratory infection
P05S02	SIMV-PRVC-PS, CPAP, (HH)	169/63 (98.3)	6	64	37.1 (127)	51	TBI
P06S02	CPAP (HH)	173/88 (114)	9.1	64	29.9 (97)	45	Trauma, postoperative ortho
P07S02[b]	SIMV-PRVC, (HH)	129/73 (98)	7.2	51	21.7 (65)	37.5	Trauma, craniotomy, pneumonia, and aspiration
P08S01[b]	SIMV-Autoflow-ASB, CPAP-ASB, (HME)	130/70 (90.0)	5.9	61	28 (90)	50	Trauma, TBI
P09S02[b]	CPAP-ASB, (HH)	135/72	11.2	56	44.2 (140)	54.5	COPD, acute renal failure, congestive heart failure, and low-grade sepsis
P10S02	SIMV-ASB, (HH)	140/62 (87)	4.2	56	23.9 (70)	42	Trauma
P11S01	Volume control-SIMV, CPAP+PS, (HME)	145/75 (91)	4.3	59	26.1 (80)	44	TBI, COPD, pneumonia
P12S01	PRVC-SIMV, CPAP, (HME)	150/64 (78)	12.8	74	26.6 (68)	37	COPD, pneumonia
	Mean	145.8/71.1	6.9	61.9	29.1 (89.3)	44.6	
	SD	15.9/11.3	2.8	7.5	6.6 (24.4)	5.3	
	Median	147.5/71.0	6.0	60.0	27.3 (87.5)	44.0	

ASB = assisted spontaneous ventilation, BiPAP = bilevel positive airway pressure, COPD = chronic obstructive pulmonary disease, CPAP = continuous positive airway pressure, HH = heater humidifier, HME = heat and moisture exchanger, PRVC = pressure regulated volume control, PS = pressure support, SIMV = synchronized intermittent-mandatory ventilation, TBI = traumatic brain injury.
[a]All patients were white male expect patient P12S01 who was white female.
[b]Died within 30 d of enrollment.
Two models of ventilators were used during the study: the Dräger Evita 4 and Maquet Servo.

data collected. This included lead deployment success, phrenic nerve integrity, stimulation breath synchrony, electrical stimulation variables, ventilation variables, blood gasses, vital signs, Critical Care Pain Observation Tool, Richmond Agitation and Sedation Scale, WOB, DT, and weaning times. User feedback on the performance and handling of the PEPNS system, the ease of use of lead preparation, lead placement, lead securement, and lead removal were also collected.

Ventilation variables were tracked and recorded over the 48-hour study period. Observed variables included tidal volume, minute ventilation, PEEP, inspiratory pressure, and other relevant values. The mode of ventilation was also recorded because stimulation was predicted to have little effect on tidal volume in flow-controlled modes but predicted to increase in pressure-controlled modes of mechanical ventilation.

PEPNS system variables, including the stimulation electrode setup, inspired/expired flow trigger sensitivities, pulse width, pulse rate, stimulation current, breath stimulation rate, and other relevant values were recorded for all stimulation sessions, including any changes made during the sessions. LabChart
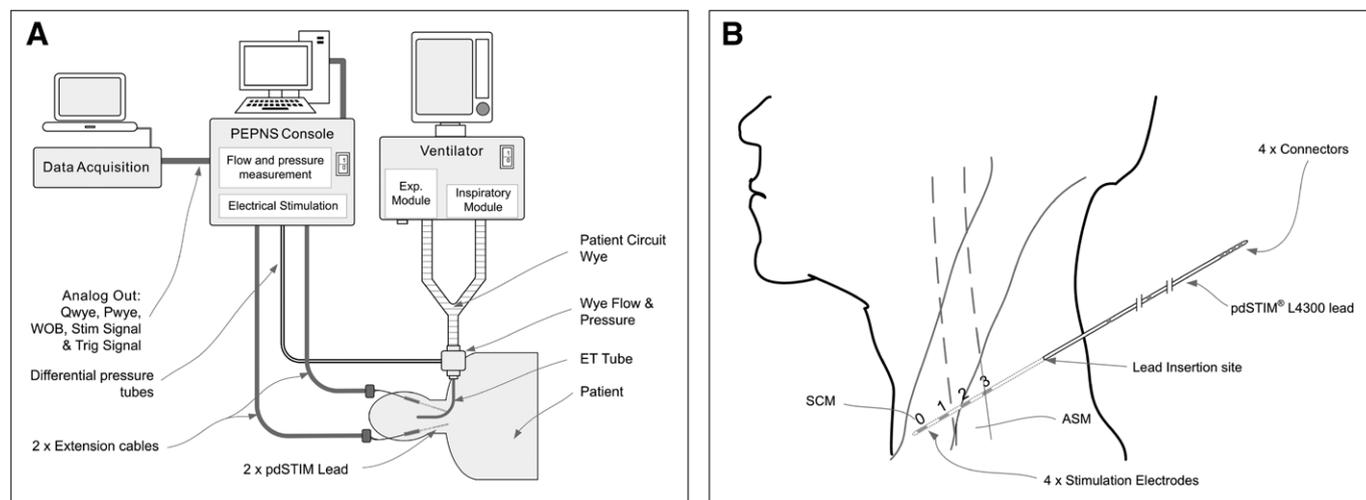
Figure 1. Percutaneous electrical phrenic nerve stimulation (PEPNS) system setup. **A**, Illustration showing PEPNS console setup connected to two L4300 pdSTIM leads in patients' neck and a wye flow sensor. PEPNS console analog outputs connected to data acquisition system. Electrical stimulation through the L4300 leads is delivered at a user-specified inspiratory count. **B**, Diagram showing pdSTIM L4300 lead positioned between sternocleidomastoid muscle (SCM) and anterior scalene muscle (ASM) muscles in the patient's neck such that the lead passes over the phrenic nerve. ETT = endotracheal tube, WOB = work of breathing.

(ADInstruments, Colorado Spring, CO) was used to record wye flow, wye pressure, WOB, Stim Signal (pulse rate) and Trigg Signal (detection of start and end of inspiration) for each of the 2-hour stimulation sessions at 1 KHz sample rate. The wye refers to the connection point where the inspiratory and expiratory limbs join. These signals, along with other calculated values such as wye pressure predicted and patient muscle effort, were displayed in real-time on the PEPNS console using knowledge of patient lung compliance and resistance as shown in **Figure 2**.

In the initial two patients, diaphragmatic compound muscle action potential (CMAP) studies were performed, and phrenic nerve latency and amplitude measured at baseline and repeated at the 30-day follow-up assessment. Using each patient as their own control, CMAP tests were performed to ensure the lead insertion procedure, subsequent electrical stimulation, and patient movement did not cause phrenic nerve injury, chemically, electrically, or physically before further patient enrollment.

Diaphragm thickness was measured using ultrasound at baseline prior to the start of the first stimulation session, 24 ± 4 and at 48 ± 4 hours after the final stimulation session using techniques described previously (15–17). Thickness measurements were performed on each hemidiaphragm at end-expiration using bedside ultrasound machines. Diaphragm thickness reaches its minimum at the end of at the end of expiration before inspiration is initiated.

Additional data collected included adverse events, device malfunctions, time to wean, type of local anesthesia and/or sedation used during the insertion procedure, the presence of tissue adhesions or signs of infection after lead removal, and how the lead insertion site was closed if necessary.

All reported adverse events and deaths were reviewed by a Clinical Events Committee in order to adjudicate the seriousness, severity, and relatedness of the event to the investigational device and/or procedure. This committee was comprised of an anesthesiologist, a critical care medicine physician, a cardiologist, and a vascular surgeon.

Statistical Analysis

The ability of the stimulation pulse to capture the diaphragm was assessed using a logistic regression model that included repeated measurements within a subject. Capture was defined as synchrony of the stimulated breath with the output variables less than 10.5 volts and WOB between 0.2 and 2.0 J/L. Synchrony was deemed successful if the lag time between start of inspiration and start of stimulation was less than 88 ms. Sample size calculations are shown in the **Supplemental Materials** (Supplemental Digital Content 1, http://links.lww.com/CCM/F345). The proportion of successful capture was analyzed using a generalized linear mixed model accounting for subject and stimulation within subject as random effects with multiple observations per subject. The null hypothesis was tested comparing the lower bound of the 95% two-sided CI for the estimated percent diaphragm capture rate to the performance goal of 80%. If the lower bound was greater than 80%, the null hypothesis was rejected, and the endpoint was considered met.

RESULTS

Fourteen patients were screened for study participation between July 2018 and February 2019. Two patients failed initial screening due to limited life expectancy. The remaining 12 subjects were enrolled in the study with the initial two patients having leads placed and assessed on the left side only. One site enrolled seven and the other five patients.

Complete patient demographic information is listed in **Table 2**. There were four deaths within the 30-day follow-up assessment. These deaths were deemed by the Clinical Events Committee to be unrelated to the investigational device/procedure. One patient was removed from diaphragm thickness analysis due to the presence of pleural effusion which obscured ultrasound imaging and the ability to accurately measure thickness.
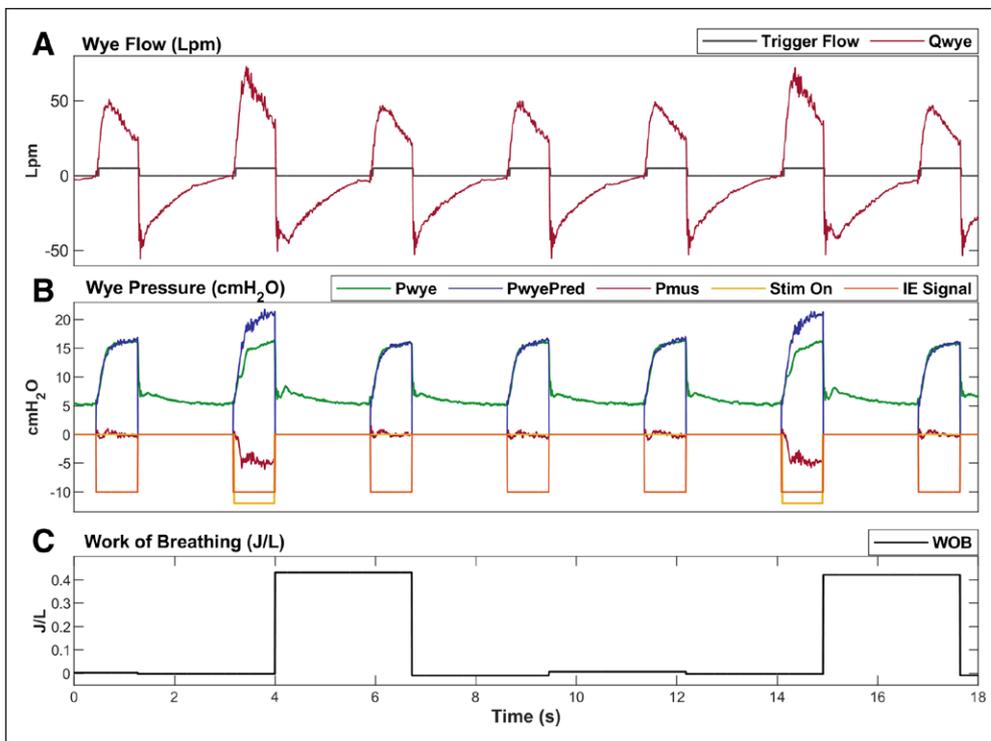
Figure 2. Data graphical display. Data collected from P0702 Stim Session no 3. **A**, Qwye in *red* (flow at the patient wye, in liters per minute); Trigger Flow in *grey* (User specified inspiratory trigger, in liters per minute [Lpm]). **B**, Pwye in *green* (measured pressure at the patient wye, in centimeters of water [cm H_2O]); PwyePred in *blue* (predicted wye pressure based upon the equation of motion, in cm H_2O); Pmus in *red* (diaphragm pressure as a result of the electrical stimulation and/or patient effort, in cm H_2O); Stim On in *yellow* (diaphragmatic stimulation active, where −12 = on and 0 = off); inspiratory expiratory (IE) signal in *orange* (where −10 = inspiration and 0 = exhalation). **C**, Work of breathing (WOB) in *black*, updated at the end of each inspiration cycle for both stimulated and unstimulated breath in joules per liter (J/L).

Two patients were predominantly ventilated with mandatory breaths even though SIMV was selected. The mandatory breath rate for these two patients equaled the measured breath rate and with triggering not observed. The median breath rate for all patients was 20.1 breaths per minute. An average of 0.25 alarms occurred per hour for the PEPNS System, primarily due to suctioning, patient coughing, water in the ventilator circuit, WOB too high, and high respiratory rate alarms.

Data analysis for the two initial patients demonstrated no procedure/device related adverse events. No difference was found between the CMAP in terms of latency and amplitude before and after electrical stimulation on either patient (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F345). Review of chest radiographs also showed no obvious change in lung volume, elevation of the diaphragm, or degree of atelectasis as a consequence of stimulation when compared with the unstimulated contralateral lung. A review of 12-lead ECG data also demonstrated no cardiac pacing, change in ECG morphology, or stimulation of the vagus nerve, which could be directly attributed to PEPNS therapy.

Data from 36,059 stimulated breaths for the 10 patients with attempted bilateral lead placement (excluding the initial two patients with left-sided lead placement only) was assessed to determine if the primary endpoints were achieved. The primary endpoints of capture of the left and/or right phrenic nerve in greater than 80% of attempts with an output variables of less than 10.5 volts and exercising the diaphragm within desired WOB limit within known safety limits of electrical stimulation were achieved (Table 1).

Secondary endpoints relating to the ultrasonic guided success of lead insertion and the ability to synchronize electrical stimulation with inspiration determined by the ability of the PEPNS System to recognize the beginning of inspiration and expiration were also achieved (Table 1). Mean cumulative time to assess the patient anatomy and successfully place nine patients with bilateral leads and one patient with a unilateral lead was 38.1 + 14.28 (range, 19–62) minutes for placement of the leads on the right side and 31.1 + 20.7 (range, 11–81) minutes for the left side. Lead deployment time decreased as clinicians gained experience with the placement procedure with larger neck circumference associated with a trend toward increased lead insertion time (**Supplemental Fig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F345).

Stimulated patients experienced a statistically significant 7.8% increase in diaphragm thickness (fractional change of 0.0783) at 24 hours versus baseline ($p = 0.0216$) and a 15% increase (fractional change of 0. 0.1507) at 48 hours versus baseline ($p = 0.0001$) (**Table 3**; and **Supplemental Table 8**, Supplemental Digital Content 1, http://links.lww.com/CCM/F345). Subanalyses of differing patient subgroups (**Supplemental Tables 9–18**, Supplemental Digital Content 1, http://links.lww.com/CCM/F345) demonstrated a significant increase in diaphragm thickness for patients with mandatory breaths versus patients with assisted/spontaneous breaths and a trend toward an increase in the stimulated side of the diaphragm versus the nonstimulated side. There was no difference in diaphragm thickness between patients with or without chronic obstructive pulmonary disease.

No serious device/procedure-related adverse events during the study. Additional study results are reported in Supplemental Digital Content 1 (http://links.lww.com/CCM/F345).

DISCUSSION

This pilot study demonstrated that the percutaneous bilateral placement of short-term, small diameter multipolar electrical

TABLE 3. Results Continued–Includes Additional Data Collected

Patient ID	No of Stim Breaths (% Stim Breaths)	Mean Breaths/Min	Mean WOB (J/L)	ΔWOB (J/L)	Mean DT (cm)	Fractional Change in Diaphragm Thickness	
						0–24 hr	0–48 hr
P01S02 Pilot	2,562 (20.95)	17.0	0.43	0.014	0.2333 L[d] 0.2100 R	−0.0571 0.0159	−0.0857 0.0635
P02S02 Pilot	3,343 (25.30)	18.3	0.79	0.066	0.2567 L[d] 0.2567 R	0.0779 0.0260	0.0000 0.0909
P03S01[a]	3,111 (23.99)	18.0	0.60	0.152	0.2530 L[d] 0.1770 R[d]	−0.0474 0.0546	0.1528 0.0979
P04S01	3,133 (24.00)	18.1	0.64	0.435	0.2167 L[d] 0.2170 R[d]	−0.0723 −0.0276	−0.0046 0.0461
P05S02	5,836 (24.37)	33.3	0.57	-0.014	0.2933 L[d] 0.2867 R	−0.0303 0.0581	0.0379 −0.0814
P06S02	4,184 (24.53)	23.7	0.75	0.390	0.1422 L[d] 0.1622 R[d]	Undetectable	
P07S02[ae]	3,557 (24.91)	19.8	0.54	0.515	0.1768 L[d] 0.1784 R[e]	0.1875 −0.0411	0.1719 0.2466
P08S01[ab]	2,407 (24.42)	13.7	0.49	0.260	0.2978 L[d] 0.1867 R[d]	0.0201 −0.0174	0.0761 0.2516
P09S02[a]	3,606 (24.72)	20.3	0.53	0.104	0.1144 L[d] 0.1311 R[d]	−0.1567 0.2679	−0.0560 0.3810
P10S02[e]	3,587 (25.13)	19.8	0.47	0.410	0.1730 L[d] 0.2263 R[d]	0.2718 0.3305	0.2718 0.2373
P11S01	3,125 (23.86)	18.2	0.53	0.353	0.1567 L[d] 0.1790 R[d]	0.2736 0.0471	0.3545 0.0638
P12S01[c]	3,630 (23.53)	21.4	0.35	0.168	0.2333 L[d] 0.2100 R[d]	0.1957 0.0757	0.2461 −0.0137
Mean		20.1	0.56	0.238	0.2070	0.0783	0.1507
SD		4.81	0.13	0.180	0.0518	0.1383	0.1376
Median		19.05	0.54	0.214	0.2100	0.0231	0.0835

DT = diaphragm thickness, L = left diaphragm, R = right diaphragm, WOB = work of breathing.

[a]Died within 30 d of enrollment.

[b]Was alive 14.9 d after weaning prior to death.

[c]Did not wean within 30 d of enrollment.

[d]Lead was placed on this side of patient's neck.

[e]Patient was ventilated with mandatory breaths only.

leads in close proximity to the phrenic nerves in the neck region using ultrasound, blunt needles, and hydrodissection is a safe and feasible approach for stimulating the diaphragm. We estimate that risk of nerve injury using this approach in a general setting would be less than the 0.03% rate reported with ultrasound-guided deep cervical and supraclavicular nerve blocks (20).

The effective capture of the phrenic nerve achieved during this study resulted from the use of a four-electrode lead design which also enabled nerve capture to be maintained over time without needing to increase the amplitude of the current delivered to the nerve. Additionally, the ability to synchronize electrical stimulation with ventilator inspiration during PEPNS therapy, the ability to control WOB within predetermined thresholds, and the stability of stimulation thresholds when patients were repositioned were also demonstrated.

The study was designed with three 2-hour stimulation sessions per day to avoid the development of proteolysis which has been reported to occur at 18 hours of diaphragmatic inactivity (8). Phrenic nerve stimulation for 30 minutes a day at normal breathing settings in a study of a single spinal cord over 8 months was shown to prevent diaphragm atrophy (21).

The increases in diaphragm thickness resulting from PEPNS therapy observed strongly support the potential efficacy of PEPNS therapy to mitigate VIDD. The increases in diaphragmatic thickness seen with PEPNS therapy may correlate with improvements in diaphragmatic function and amelioration of VIDD. This may result in shorter weaning times and improved measures of diaphragmatic strength in future studies. The ability of PEPNS therapy to mobilize the diaphragm is also likely to improve aeration in the lung bases. This point is borne out by the fact that despite using the same driving pressures, tidal volumes for stimulated breaths increased by 34.6% ± 16.9% (**Supplemental Table 19**, Supplemental Digital Content 1, http://links.lww.com/CCM/F345). Since the resultant increase in tidal volumes seen as a consequence of phrenic nerve stimulation comes at no "pressure cost", this therapy could be of significant benefit to patients who have significant air leaks.

Patients who were exclusively ventilated using mandatory breaths showed a greater increase in diaphragm thickness compared with patients who were breathing in assist or spontaneous modes of ventilation. This is in line with expectations because assist and spontaneous breath types are known to increase or maintain diaphragm strength and thickness. With this in mind, PEPNS therapy could also potentially be a worthwhile tool in patients with severe traumatic brain injury who require prolonged periods of deep sedation and consequent mandatory ventilation modes. In patients with high spinal injuries, percutaneous phrenic nerve stimulation may maintain diaphragmatic strength and could become a potential weaning tool.

Mean fractional changes in diaphragmatic thickness were found to correlate well with the mean difference in WOB between stimulated and unstimulated breaths suggesting higher WOB levels may lead to greater increases in diaphragm thickness (**Supplemental Fig. 12**, Supplemental Digital Content 1, http://links.lww.com/CCM/F345).

The present study has several limitations. These include small sample size, the short duration of electrical stimulation, and the lack of a control group, although the first two patients acted as their own controls in terms of CMAP studies. Changes in diaphragmatic thickness could be reinforced by measuring changes in shortening fraction or diaphragm thickness variation between inspiration and expiration. The concurrent use of electrical impedance tomography could be used to demonstrate regional changes in ventilation in response to phrenic nerve stimulation. Since the majority of patients enrolled were admitted for trauma and traumatic brain injury, generalization of our results to other patient populations should be avoided until broader clinical studies with this technology are completed.

Percutaneous placement of electrical phrenic nerve stimulation leads in a patient's neck region represents a promising new approach to maintaining diaphragmatic work for patients on mechanical ventilation. The ability to place the pdSTIM leads at the patient's bedside and to synchronize electrical stimulation of the phrenic nerve with inspiration while maintaining WOB suggests PEPNS therapy may offer a future option for preventing or treating VIDD and reducing weaning times for patients on ventilators.

CONCLUSIONS

The present study demonstrated the ability to safely and successfully place percutaneous multipolar leads in the anatomical region of the neck close to phrenic nerves in patients on mechanical ventilation. It also demonstrated the feasibility of using this approach to synchronize electrical stimulation with inspiration while maintaining WOB within defined limits. While promising, additional clinical studies are needed, including prospective assessment with a control group as a comparator.

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