**eAppendix.**
Neuromuscular Rehabilitation by Diaphragm Pacemakers in Pompe Disease

## Respiratory Muscle Tests

Each patient underwent preoperative respiratory muscle testing to determine the severity of the respiratory muscle dysfunction and his or her eligibility for diaphragm pacing. Postoperatively, electrophysiological and functional testing were conducted at each patient's initial session for diaphragm conditioning and then at periodic intervals for follow-up appointments. Ventilatory parameters were recorded with a capnograph system (NICO, Philips-Respironics, Murrysville, Pennsylvania), and testing was conducted per American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[1]

**Maximal Inspiratory Pressure.** Maximal inspiratory pressure was assessed while sitting upright using an inspiratory occlusion technique validated for patients who are mechanically ventilated.[2,3] The ventilator was removed, and a pressure transducer and one-way valve were placed directly onto the airway opening (either the tracheostomy tube or a sealed mask). The valve permitted exhalation but prevented any inspiratory airflow. The test was administered for 20 seconds and repeated 3 times. The best effort was recorded. During the preoperative tests in adults (patients 1 and 3), transdiaphragmatic pressure measurements were captured using gastric and esophageal pressure microtransducers (Millar Inc, Houston, Texas).

**Evoked Phrenic Motor Potentials.** Supramaximal anterolateral phrenic magnetic stimulation was recorded in patients 1 and 3 to determine whether the phrenic nerves could be stimulated. The resulting phrenic motor latencies and the durations and amplitudes of the resulting compound muscle action potentials were recorded. The patient was removed briefly from the ventilator, and twitch stimulation was delivered at end-exhalation with the airway occluded. At least 5 supramaximal stimulations were carried out. The best 3 twitch maximal transdiaphragmatic pressure measurements were averaged and compared with published values.[4]

**Breathing Pattern Assessment.** The breathing pattern was recorded using a combined pneumotachograph/capnograph placed in series with the mechanical ventilator (Capnostat, Philips-Respironics, Murrysville, Pennsylvania). Measurements were initiated in an upright position in the morning, after patients rested on full ventilator support overnight.

**Off-Ventilator Endurance Time.** At the start of the test, patients were seated upright and in a rested state. The pneumotachograph/capnograph was connected to the end of the tracheostomy tube. After recording the resting breathing pattern, the ventilator was disconnected from the patient, and the first unassisted breath was counted as the zero time point. The off-ventilator endurance was timed while patients breathed without assistance until one or more of the following signs of impending failure occurred: increase in heart rate $\geq$30 bpm from resting or heart rate 80% of age-predicted maximum; change in systolic blood pressure 30 mm Hg from rest; oxygen saturation sustained below 92% for at least 2 minutes; end-tidal carbon dioxide levels more than 50 mm Hg or increased 10 mm Hg above resting; respiratory rate higher than 40 breaths per minute sustained for 2 minutes (50 breaths per minute in children younger than 8 years); junctional or ventricular dysrhythmias; evidence of impeding fatigue (eg, predominant accessory muscle use, substernal retraction, sternomastoid muscle activation, paradoxical breathing, nasal flaring); diaphoresis or pallor changes; or patient felt unable to continue and requested assisted ventilation.

**Diaphragm Descent.** The diaphragm descent fluoroscopic examination was administered as part of the determination for candidacy for diaphragm pacing. Patients were positioned as upright as possible, and diaphragmatic movement was recorded during resting breathing on the ventilator. The patient was then removed from mechanical ventilation and encouraged to sniff as forcefully as possible. Three maximal sniffs were obtained, with at least 2 minutes of rest on the ventilator between repetitions.

## Preoperative Inspiratory Muscle Exercises

During the preoperative evaluation period, patients were given an inspiratory muscle exercise prescription, which consisted of inspiratory muscle strength training and spontaneous breathing trials on reduced ventilator settings. Inspiratory muscle strength training was administered with the Threshold PEP trainer (Philips-Respironics) connected directly to the tracheostomy tube or ventilation mask opening. The training device contains a poppet valve held closed by a spring, which required patients to produce enough pressure during inspiration to overcome the tension of the spring (Fig. S1). This exercise prescription has been reported to increase maximal inspiratory pressure and facilitate ventilator weaning in adults who are difficult to wean and children without neuromuscular diseases.[5,6] Within a training session, 4 sets of 6 to 10 breaths were administered, with 2 to 3 minutes of rest between sets. Patients completed 3 to 5 training sessions weekly, and they were instructed to complete the exercises independently or with caregiver assistance.

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In addition, spontaneous breathing trials were completed at least 5 days per week. The patient's pressure support was progressively lowered in 20% increments to identify the lowest support where the patient could preserve minute ventilation for at least 20 minutes with stable vital signs. There was considerable variability in each patient's tolerance for reduced support. Patient 2 was able to complete the spontaneous breathing trials for 30 to 60 minutes without mechanical ventilation support. Patients 1 and 3 used synchronous intermittent mandatory ventilation at a reduced backup rate (intermittent mandatory ventilation of 2–6 breaths) and peak inspiratory pressure (20%–30% reduction from resting peak inspiratory pressure) for 20 to 60 minutes.

## Diaphragm Pacing Settings

The NeuRx Diaphragm Pacing System (DPS, Synapse Biomedical Inc, Oberlin, Ohio) can be programmed to coordinate with spontaneous breathing on reduced or no mechanical ventilation support. The optimal pacer settings differed slightly for each patient. Generally speaking, low-frequency, short pulse-width stimulations were delivered at the highest comfortable amplitude that elicited a gain in tidal volume. The biphasic pulse stimulus for each of the 4 stimulation channels was programmed separately for the following parameters:

**Power.** Specific channels can be turned on and off, as indicated.

**Amplitude.** The pulse amplitude (5–25 mA) is the intensity (in milliamperes) of each stimulus pulse. Amplitudes of 25 mA are well tolerated in patients with high cervical spinal cord injury with sensory impairments.[7] Because our case patients retained full sensation, the initial amplitude was limited to the highest nonpainful intensity, which occurred between 5 and 8 mA.

**Pulse width.** The pulse width (20–200 microseconds) reflects the duration (in microseconds) of stimulation. Changes in pulse width within the clinically significant range do not elicit large fluctuations in the size of the motor units recruited (somewhat smaller diameter fibers at higher pulse widths).[8] Although pulse width does appreciably influence fatigability within the programmable range of the DPS, a longer pulse width is associated with greater evoked force and larger depth of penetration, when the amplitude is held constant.[9]

In addition to the channel-specific stimulation settings, the general timing of the stimulation could be adjusted with the following parameters:

**Frequency.** The pulse frequency (5–50 Hz) was maintained between 11 and 15 Hz in the case patients. In the canine model of chronic phrenic pacing, high-frequency stimulation elicited Z-band streaming and contractile dysfunction, but low-frequency stimulation was not found to be injurious and promoted greater oxidative function in muscle fibers.[10] The manufacturer recommends that stimulus frequency not exceed 20 Hz for chronic stimulation.

**Inspiration time.** The inspiration time (0.8–1.5 second) was set to the length needed to facilitate diaphragm contraction during inspiration and rest during exhalation. Considerations for the DPS inspiration time included the patient's inspiratory duty cycle and tidal volume required to maintain minute ventilation.

**Breath rate.** The DPS breath rate (8–18 breaths per minute) was set to a frequency that matched the patient's comfortable spontaneous respiratory rate. During early phases of conditioning, when patients could not tolerate a lengthy removal from mechanical ventilation, either synchronous intermittent mandatory ventilation or spontaneous ventilator modes were used, enabling the patient to trigger the ventilator with the pacer. The DPS rate was set to at least 2 breaths per minute faster than the patient's backup rate. If the patient was able to tolerate unassisted breathing with a spontaneous respiratory rate over 18 breaths per minute, the DPS was set to match the patient's spontaneous rate in a 2:1 or 3:1 synchronized fashion (eg, a DPS rate of 11 breaths per minute would be used with a spontaneous respiratory rate of 22 breaths per minute).

**Ramp.** The ramp setting (0–10) enabled a gradual lengthening of the pulse width at the pulse onset. Patients reported that this more gradual contraction felt more natural, and pulse settings between 3 and 6 were typically programmed.

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## Long-Term Maintenance and Repair of Pacer Leads

The internal leads are secured and coiled subcutaneously to prevent disruption, but the leads are susceptible to damage between the exit site from the skin and the connection to the stimulator block. All of the patients required some long-term maintenance to the external lead segments due to fraying or breakage. After 16 months, patient 1 experienced breakage of the ground lead at the exterior connection to the stimulator block. Patient 2 also experienced ground lead failure after 8 months of pacing. Lead 2 was damaged in patient 3 within the first postoperative week and in the fourth month after implantation. In each of these instances, these minor repairs were made on-site without a need for sedation.

Additional fraying of multiple individual leads in patient 2 resulted in a repair of the external lead block and ground lead replacement after 2 years. Due to patient 2's young age, this procedure was performed under sedation. This repair resulted in a transient seroma around the umbilicus that resolved. External lead breakage may be more common in patients such as ours, who retain some residual limb function.

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**Table S1.**
Medical Course of Patient 1[a]

| Event | Initial Evaluation (4+ y MV) | 4 wk IMST | Pacer Implant | 1 wk | 1 mo | 3 mo | Present |
|---|---|---|---|---|---|---|---|
| Time (relative to pacer implant) | –6 wk | –2 wk | | +1 wk | +35 d | +80 d | +3 y |
| Serum CK (U/L) | | | 293 | 198 | 262 | | |
| Off-ventilator tolerance/d | 2.1 min | 2 min | | 1.8 min | 4 min | 8 h | 12+ h |
| Spontaneous $V_T$ (mL/kg) | 4.1 | 4.2 | | 3.3 | 4.3 paced | 5.7 paced | |
| $V_E$ (L/min) | 4.2 | 4.2 | | 6.6 | 7.3 paced | 10.2 paced | |
| Pacing tolerance (h/d) | | | 0 | 2 | 24 | 24 | 24 |
| MIP (cm $H_2O$) | –38 | –32 | | –22 | –24 | –31 | |

[a] Despite chronic ERT and immunosuppression, patient 1 could tolerate only about 2 minutes of unassisted breathing without MV and was chronically ventilator-dependent for >4 years upon transfer to our care. The goals for diaphragm conditioning during the first postoperative month included weaning to minimal daytime ventilator settings and continuous diaphragm pacing. After postoperative day 35, he discharged to inpatient rehabilitation in his home state, where the conditioning regimen emphasized progressive, paced breathing without MV. When the patient was discharged to home on postoperative day 65, he could spend 8 to 10 hours pacing without MV. At 3 years, the patient remains weaned from MV support when awake. CK=creatine kinase, ERT=enzyme replacement therapy, IMST=inspiratory muscle strength training, MIP=maximal inspiratory pressure, MV=mechanical ventilation, $V_T$=unassisted tidal volume, $V_E$=unassisted minute ventilation.

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**Table S2.**
Medical Course of Patient 2[a]

| Event | Diagnosis and ERT Baseline | 3 y ERT and Immune Modulation | Tracheostomy and MV | 8 wk MV, 4 wk IMST | Pacer Implant | 1 wk | 6 wk | 6 mo | Present |
|---|---|---|---|---|---|---|---|---|---|
| Time (relative to pacer implant) | –3.2 y | –3 mo | –2 mo | –1 d | | +7 d | +50 d | 5.5 mo | +2.4 y |
| Serum CK (U/L) | 560 | 409 | | 949 | 806 | 876 | 1,822 | | |
| M-mode LV mass (Z) | 9.22 | 7.27 | 6.59 | | | | 6.01 | 3.38 | 2.4 |
| Off-ventilator tolerance | | NIV, 20 min | 10 min | 60 min | | 60 min | 12 h | 12 h | 16–17 h |
| Spontaneous $V_T$ (mL/kg) | | 3.8 | | 5.0 | | 5.3 paced | 6.1 paced | 7.7 paced | |
| $V_E$ (L/min) | | | | 3.6 | | 5.5 | 4.6 | 5.5 | |
| Pacing tolerance (h/d) | | | | | 0 | 2 | 24 | 24 | 4–6 |
| MIP (cm $H_2O$) | | –28 | –35 | –65 | | | –53 | –61 | –78 |

[a]Patient 2 had hypertrophic cardiomyopathy and respiratory compromise that was unresponsive to chronic ERT and immunosuppression. Neither NIV nor tracheostomy reduced reversed ventilatory muscle compromise. After 1 month of pacing, she was weaned from MV during most daytime hours and remains weaned during waking hours >2 years later. Cardiac function also has improved following in the 2 years since pacing. CK=creatine kinase, ERT=enzyme replacement therapy, IMST=inspiratory muscle strength training, MIP=maximal inspiratory pressure, MV=mechanical ventilation, NIV=noninvasive ventilation, $V_T$=unassisted tidal volume, $V_E$=unassisted minute ventilation, LV=left ventricular.

**Table S3.**
Medical Course of Patient 3[a]

| Event | Initial Evaluation (5+ y NIV) | After 14 wk IMST | Pacer Implant | 1 wk | 6 wk | 12 wk | 1 y |
|---|---|---|---|---|---|---|---|
| Time (relative to pacer implant) | –4.5 mo | –7 d | | +7 d | +45 d | 90 d | 1 y |
| Resting $Paco_2$ (mm Hg) | 44 | | 42.8 | 43.6 | 42.2 | | |
| Off-ventilator tolerance | 0.6 min | 1.1 min | | 0.25 min | 0.6 min | 50–60 min | 10–12 min |
| Peak inspiratory pressure support | 33 cm $H_2O$ NIV | 33 cm $H_2O$ NIV | 33 cm $H_2O$ invasive | 30 cm $H_2O$ invasive | 29 cm $H_2O$ invasive | 26 cm $H_2O$ invasive | 16 cm $H_2O$ invasive |
| Spontaneous $V_T$ (mL/kg) | 2 | 2.1 | | 1.0 | 1.1 | | |
| $V_E$ (L/min) | 5.4 | 5.4 | | 5.4 | 4.4 | | |
| Pacing tolerance (h/d) | | | 0 | 3 | 24 | 24 | 24 |
| MIP (cm $H_2O$) | –13.5 | –12.8 | | –8.5 | –12.5 | | |

[a]The patient required continuous, high-level NIV for >5 years prior to pacing. At postoperative day 8, he was tracheostomized to facilitate secretion clearance in the presence of severe tracheal and bronchial malacia. The patient was discharged to inpatient rehabilitation in his home state at postoperative day 50 and was discharged to home on postoperative day 75. Due to the severe malacia, the emphasis of patient 3's weaning strategy was redirected from daily independent breathing trials to slow weans at progressively lower positive pressure support during all waking hours. Patient 3 resumed ERT 10 months postoperatively. The patient can achieve independent airway clearance, daytime support is 40% lower from early postop requirements, and progress with weaning has not plateaued. ERT=enzyme replacement therapy, IMST=inspiratory muscle strength training, MIP=maximal inspiratory pressure, MV=mechanical ventilation, NIV=noninvasive ventilation, $Paco_2$=arterial pressure of carbon dioxide obtained overnight, $V_T$=unassisted tidal volume, $V_E$=unassisted minute ventilation.

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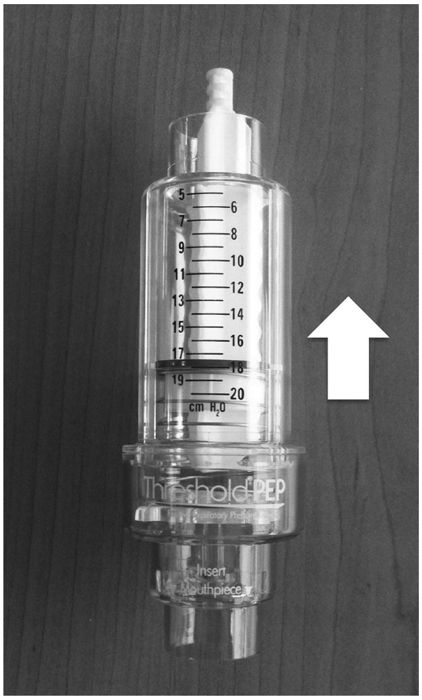


**Figure S1.**
Inspiratory muscle strength training device. Patients trained with a pressure threshold device attached directly to the tracheostomy tube or ventilator mask. The training stimulus was provided by the tension of an adjustable spring, which held the inspiratory valve of the device closed. To receive inspiratory airflow (direction noted by arrow), patients were required to generate a minimum inspiratory pressure to overcome the tension of the spring and open the inspiratory valve. Exhalation was not resisted. Training sessions occurred 3 to 5 days per week, and consisted of 4 sets of 8 to 12 breaths.


**Figure S2.**
Diaphragm pacing external pulse generator. The pulse generator connected to the pacer leads, via a stimulator connector block secured to the patient's right upper quadrant. The external connection permits removal of the pulse generator for transfers and hygienic activities, as needed. The pulse generator was initially programmed in the operating department. Stimulus settings, primarily the amplitude and pulse width, were adjusted weekly for the first 30 days and then monthly for the first 90 days.