

DIAPHRAGM PACING AND NONINVASIVE RESPIRATORY MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS/MOTOR NEURON DISEASE

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ABSTRACT: *Introduction:* Although it is known that continuous noninvasive ventilation (CNIV) can prolong life in amyotrophic lateral sclerosis/motor neuron disease (ALS/MND), in this study we explore similar claims for diaphragm pacing (DP). *Methods:* NIV and DP users' vital capacities (VCs) over time and duration of NIV and CNIV dependence were analyzed for 354 non-DP and 8 DP ALS/MND patients. *Results:* Patients had a higher rate of monthly VC decline before NIV use ($5.1 \pm 7.6\%$) than during NIV use ($2.5 \pm 3.6\%$) ($P < 0.01$, 95% CI 0.84–4.5); the decline for 4 DP users was 3.7–20%. Fifty-five ALS/MND patients used part-time NIV for 19.9 ± 27.6 months until tracheostomy/death, whereas 113 others used it for 10.9 ± 10.5 months until CNIV dependence for another 12.8 ± 16.2 months. After placement, 7 DP users were CNIV dependent in 8.0 ± 7.0 months, whereas 6 underwent tracheostomy/died in 18.2 ± 13.7 months. *Conclusions:* CNIV prolonged the survival of 113 of the 354 non-DP and 6 DP ALS/MND patients by 12.8 and 10.2 months, respectively. DP provided no benefit on VC or mechanical ventilation-free survival.

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A 1999 consensus group of the National Association for Medical Direction of Respiratory Care recommended introducing nocturnal bi-level positive airway pressure (PAP) for patients with amyotrophic lateral sclerosis (ALS) once forced vital capacity (VC) had declined to 50% of normal.¹ This 50% figure is now also being used as an indication to implant diaphragm pacing (DP; NeuRx DPS; Synapse Biomedical, Inc., Columbus, Ohio) in the hopes of preserving diaphragm strength, decreasing the rate of loss of vital capacity (VC), and prolonging “mechanical ventilation-free” survival.^{2,3} Bi-level PAP and DP indications are being based on VC in the supine position, irrespective of the presence or absence of symptoms of hypoventilation.³ Neither bi-level PAP nor DP have been cited to have been used for full ventilatory support. Indeed, intramuscular DP was explicitly noted to not serve any role in “patients with lower MNDs,” because “intact bilateral phrenic nerve function” is required. Intact lower motor neuron input to the

diaphragm has never been reported to occur in ALS.⁴

For patients with ALS, VC was reported to decline in a relatively linear manner after an initial inflection for 34 patients.⁵ It has been suggested that DP use can decrease the rate of loss of VC by $\geq 50\%$.³ However, most of the patients in the DP study were also using bi-level PAP, a form of NIV for nocturnal use but impractical for continuous NIV for ventilator support (CNIV).⁶ Further, bi-level PAP, unlike volume cycling, does not permit air stacking⁷ to raise voice volume or cough flows.

A review of the literature reveals that NIV use alone has been reported to be associated with a decrease in the rate of loss of VC by $\geq 50\%$. Bourke et al. reported a VC decline of 2.52% per month changing to 1.09% with bi-level PAP use⁸; For Lo Coco et al. 2.92 to 0.5%⁹ and for Kleopa et al. 4.8% to 3.5%.² However, a study in which NIV was not used at all also cited a decrease in rate of loss of VC by 50% from 3.5%/month once the VC had decreased to $< 55\%$ of predicted normal.¹⁰ Thus, we compared the rate of loss of VC for our DP and NIV users.

Although patients with ALS/MND can die from ventilatory failure, it can be averted with CNIV in patients with functional bulbar-innervated (bulbar) musculature, even when all autonomous ability to breathe is lost.¹¹ However, once bulbar impairment results in a decrease in oxyhemoglobin saturation baseline of $< 95\%$ because of saliva aspiration, 90% of such patients develop acute respiratory failure (ARF) or undergo tracheotomy within 2 months, irrespective of NIV use.¹¹

Phrenic nerve pacing was described by Glenn et al. for high-level spinal cord injury (SCI) patients more than 50 years ago.¹² More recently, direct DP has also successfully supported lung ventilation for SCI patients with physiologically intact peripheral nerves and diaphragms and little or no VC.^{3,4} In 2009, Onders et al. extended its application to patients with ALS/MND with 36 of 38 patients having implantation despite having VCs of $> 50\%$ and not having gastrostomy tubes. These requirements eliminated patients with severe bulbar dysfunction and any future resort to tracheostomy that would result from extubation failures after gastrostomy tube placement. This could improve tracheostomy-free outcomes that may be

Abbreviations: ALS, amyotrophic lateral sclerosis; ANOVA, analysis of variance; ARF, acute respiratory failure; CNIV, continuous noninvasive intermittent positive pressure ventilation; DP, diaphragm pacing; MND, motor neuron disease; NIV, noninvasive positive pressure ventilation; PAP, positive airway pressure; Pt-NIV, part-time noninvasive positive pressure ventilation; SCI, spinal cord injury; TT, tracheostomy; VC, vital capacity

Key words: amyotrophic lateral sclerosis, diaphragm pacing, motor neuron disease, neuromuscular disease, noninvasive mechanical ventilation, survival, vital capacity

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attributed to DP placement.³ They also reported that the pre-implantation VC rate of decline of 2.4%/month decreased to 0.9% post-implantation and extrapolated this to mean 2 additional “mechanical ventilation-free” years or, more specifically, survival without ventilatory support via an indwelling tracheostomy tube. A more recent study reported a VC drop-off after DP implantation of 2.3% per month with half of the patients using bi-level PAP.¹³

The purpose of this study was to compare VC decline and ventilator-free survival for 8 consecutively referred patients after DP placement with our general ALS/MND population. Whereas “mechanical ventilation” is typically meant to be via tracheostomy, it can also be provided as CNIV without requiring hospitalization or the development of ARF.¹¹

METHODS

This retrospective analysis was approved by our institutional review board. We included all patients referred from March 1996 (the beginning of the computerization of our medical records) through December 2011 to a neuromuscular disease clinic who were diagnosed with rapidly progressive ALS/MND on the basis of typical clinical and electrodiagnostic findings in the absence of any other etiology for MND, such as post-poliomyelitis, spinal muscular atrophy, or prolonged clinical course, as indicated by a lack of need for continuous ventilator dependence 10 years from onset.

Demographic information and clinical course were recorded, including duration from symptom onset to physician presentation or diagnosis, to part-time (8–23 hours/day) NIV use, to need for CNIV with little or no autonomous ability to breathe, and to tracheotomy or death. The VC was measured at every patient visit. The DP placement date was noted. For measurement of DP-delivered volumes, the patients were instructed to relax and let the pacer “breathe” for them while exhaling passively into a spirometer. Once tidal volumes were observed to vary by <10% with no observed accessory muscle or diaphragm use, the average DP-provided volume was determined from 3 consecutive DP cycles. The DP was intermittently turned off to verify absence of autonomous breathing. Thus, the DP-provided lung volumes were determined from functional residual capacity and were compared with VC.

Rate of VC decline from VC inflection point to CNIV dependence, tracheostomy, death, or last visit was determined. Because most ventilator users were visited monthly by the same respiratory home-care company, information about their venti-

Table 1. Characteristics of the non-DP ALS/MND patients.

Criterion	n	Months
		[mean ± SD (range)]
Symptom onset to diagnosis	354	10.4 ± 19.1 (0–252)
Symptom onset to endpoint	155	49.4 ± 35.3 (3–196)
Symptom onset to Pt-NIV	216	32.4 ± 24.5 (0–134)
Diagnosis to endpoint	155	39.0 ± 33.2 (1–181)
Diagnosis to Pt-NIV	216	31.7 ± 24.7 (0–134)
Pt-NIV to TT/death	55	19.9 ± 27.6 (1–119)
Pt-NIV to CNIV	113	10.9 ± 10.5 (0–60)
Duration of CNIV	113	12.8 ± 16.2 (1–84)
CNIV only without Pt-NIV	6	9.3 ± 6.6 (1–18)
CNIV use >24 months	15	46.7 ± 18.9 (28–84)

Onset of symptoms was determined by report of onset of fasciculations, muscle cramps, extremity weakness, or orthopnea, or speech, swallowing, or breathing difficulties. Pt-NIV, part-time bi-level positive airway pressure or intermittent positive pressure ventilation 8–23 hours/day (endpoint: CNIV, tracheostomy, or death). CNIV, continuous (24 hours/day) dependence on NIV.

lator use, or death with return of the respiratory equipment, was available after the last office visit. Patients who had other home-care companies and whom we had not seen for >3 months were telephoned for follow-up information. Outliers who had >30% of predicted normal VC 10 years after symptom onset were excluded from the analysis.

Indicators of bulbar muscle integrity were air stacking ability and presence or absence of gastrostomy. Air stacking ability provides a quantitative, objective, and reproducible assessment of glottis integrity (active glottis closure) and, therefore, bulbar-innervated muscle function.⁷

Statistical analyses of the changes in percent of predicted VC for patients who were not using ventilator/DP or those who were using ventilator/DP before and during use were done using analysis of variance (ANOVA) with the Tukey *post hoc* analysis and are presented as mean ± standard deviation.

RESULTS

Of 368 ALS/MND patients, 7 outliers had a VC of >30% at 10 years after symptom onset, and their 15 VC data points were excluded. Two of the 7 had survived by CNIV dependence for 2 and 5 years, respectively.

The long-term outcomes of 354 ALS/MND without DP are summarized in Table 1. None of the 241 patients who did not progress to CNIV dependence could air stack when they were hypercapnic, whereas all but 2 (99%) of the CNIV users could. Hypercapnic bulbar ALS/MND patients who were unable to use NIV or air stack (close the glottis) were at high risk for severe aspiration and ARF.¹¹

A total of 988 VC measurements, including 698 for the NIV users, were recorded. Fifty-five ALS/MND patients used part-time NIV for 19.9 ± 27.6 months until tracheostomy or death. One hundred

Table 2. Characteristics of 8 patients with diaphragm pacing (DP).

Patient	Age at onset (y)	Onset of symptoms to physician presentation (mo)	Onset of symptoms to DP (mo)	Onset to wheelchair dependence (mo)	Onset to NIV (PM) (mo)	Onset to NIV AM+PM (mo)	DP to CNIV (mo)	DP to TT/death (mo)
1	54	8	52	28	23	31	2	17
2	58	5	45	39	25	51	22	44
3	47	7	17	10*	No NIV	No NIV	No NIV	17
4 [†]	59	14	43	46	37	40	2	—
5	51	9	20 [‡]	21	11	22	6	17
6	57	19	50	64	52	60	10	—
7	55	6	16	9	16	23	10	10
8	70	7	24	N/A	24	26	4	4

Onset of symptoms was determined by report of onset of fasciculations, muscle cramps, extremity weakness, or orthopnea, or speech, swallowing, or breathing difficulties. DP, diaphragm pacing; NIV, non-invasive positive pressure mechanical ventilation; PM, night-time ventilation; AM+PM, up to 23 hours/day; CNIV, continuous NIV; TT, tracheostomy.

*Had wheelchair, but could walk until death.

[†]Stopped using DP after 2 months because it was ineffective and caused pain.

[‡]VC 65% at DP placement.

thirteen other patients used part-time NIV for 10.9 ± 10.5 months, then CNIV for 12.8 ± 16.2 months, and 12 are still using it. The pre-NIV VC rate of decline for the 216 NIV users was $5.1 \pm 7.6\%$ per month, decreasing to $2.5 \pm 3.6\%$ ($P < 0.01$, 95% confidence interval 0.84–4.5) during NIV use. The 78 patients who began NIV at our center did so with a mean VC of $44.0 \pm 24.0\%$ (0–114%) of predicted. Sixty-four of the ALS/MND patients, after being introduced to NIV in the outpatient clinic, eventually became dependent on it continuously without being hospitalized.

The outcomes of the 8 ALS/MND patients who underwent DP placement are summarized in Table 2. At our initial evaluation, all 8 spoke clearly, swallowed food without difficulty, and were able to air stack⁷; thus, they had excellent glottis and bulbar muscle function at the time of DP placement. Despite this, 5 of 8 had gastrostomy tubes placed as mandatory procedures along with DP. Two of the 5 did not use the tubes and remained “nonbulbar” despite eventually becoming CNIV dependent, including 1 who still has not used the gastrostomy.

Six of the 8 DP patients reported that they had to turn down or turn off the DP because of shoulder and abdominal pain, and 4 discontinued it permanently because of ineffectiveness and pain. One discontinued it after 2 months of use, after which her VC temporarily increased by 15%. The 7 DP patients who were offered NIV became continuously dependent on it at 2–22 (mean 8.0 ± 7.0) months after DP placement and died or underwent tracheotomy 18.2 ± 13.7 months from DP placement. Thus, the lives of these 7 DP users were prolonged for a mean of 10.2 months (difference of 18.2 and 8.0 months) by continuous mechanical ventilation (Table 2). None of these patients could turn off the ventilator or use it less with the use of DP. Five of the 8 DP patients died

at 13.0 ± 5.8 months from placement. Mechanical ventilation/tracheostomy-free survival was only 8.0 ± 7.0 months after DP placement despite a VC $\geq 50\%$ at the time of placement^{11,14}; only 1 DP user is still alive without a tracheostomy at 10 months post-placement, but he too requires CNIV for survival. The 6 DP patients died or underwent tracheotomy at 18.2 ± 13.7 months as compared with 55 part-time-only NIV users in our study who survived without tracheostomy for 19.9 ± 27.6 (0–119) months from onset of NIV despite beginning NIV with a lower mean VC of $44.0 \pm 24.0\%$.

For 4 CNIV-dependent patients with DP, the DP-generated tidal volumes from functional residual capacity of 110, 80, 40, and 20 ml represented between 10% and 25% of their VCs at the time. Once 4 of our patients required CNIV to survive, DP was being used to “flutter” the diaphragm about 30 times per minute. However, because the DP was dyssynchronous with the patients’ breathing, there was no relief from ventilator use, any benefit on alveolar ventilation, or any apparent benefit on VC by “diaphragm conditioning.” Four patients who had multiple VC data points during DP use had VC rates of decline of 3.7%, 7.2%, 11%, and 20% (mean 10.5%) per month, respectively, for 13 data points.

DISCUSSION

As described previously, the VC drop-off rate decreased by 50% for those who used NIV. However, the 4 DP users with multiple post-DP placement VC data points had VC drop-off rates that averaged 4 times more than our non-DP patients and 10 times more than in the study by Onders and colleagues.³ The rates of VC decrease in their patients, both before and after DP placement, were less than in our general ALS population, thereby denoting a more mildly affected

population. This can be explained by more severely affected patients being selected out by eliminating those with severe bulbar dysfunction. Thus, caution should be taken before suggesting that DP can benefit pulmonary function.

Three other claims of possible benefit from DP include: delay of need for “mechanical ventilation” (tracheostomy) or death by 24 months; increasing diaphragm strength for which there is currently a multicenter study underway; and improvement in sleep quality.³ To accomplish the first 2 claims, however, DP must provide volumes greater than the patient’s inspiratory capacity.³ That is, strength is increased more by active rather than electrical contraction of muscle when muscle force is greater by active contraction than by electrical stimulation.^{15,16} In our study, DP volumes did not exceed 25% of the patients’ inspiratory capacity, and therefore they were far inferior to autonomous ability. Thus, no freedom from ventilator use could be achieved by DP. Once CNIV was required, DP contributed nothing to minute ventilation, so the patients had to grab a mouthpiece for intermittent positive pressure volumes as frequently with DP off as with it on.

Besides the failure to systematically introduce NIV for eventual CNIV, the poorer survival using DP may be due to DP-induced myopathic deterioration of the diaphragm,^{15–17} NIV use at less than full ventilatory support settings, and failure to introduce mechanically assisted coughing.¹¹ One ALS patient with normal bulbar function and no respiratory symptoms had DP placed at 68 years of age. The next month, CPAP, which is inappropriate for hypercapnic ALS/MND patients, was prescribed for this patient, who “could not tolerate it.” She remained nonbulbar and able to walk until dying suddenly 4 months later, never having been offered NIV. Her husband said she had a very low voice and, during her final week, “we could barely hear her.” Indeed, comparable to our success in managing ventilator dependence without tracheostomy or even hospitalization in many cases (Table 1), Sancho et al. reported that 22 of 88 ALS/MND patients (25%) became CNIV dependent for 7.8 ± 8.1 (range 1–36) months before undergoing tracheotomy, and some did not require hospitalization.^{14,18} Thus, claims of survival prolongation by DP use resulted from concomitant CNIV.

Considering sleep quality, sleep efficiency was reportedly increased by 9% in ALS/MND patients with VCs of 50–85% of normal with DP. However, there was no attempt to rule out a placebo or “first night” effect, and the apnea–hypopnea index and other sleep parameters were not improved.¹³ The *MDA/ALS Newsmagazine* [“For 1 man with ALS, diaphragm pacing system means ‘a life better lived’,”

2012;17(1):6–7] reported an orthopedic patient with >50% of predicted VC who used DP instead of NIV to reverse rapid eye movement sleep apneas for several months. However, because we observed that DP could not provide tidal volumes of >25% inspiratory capacity, while the VC remains >2 L, DP may be adequate for normal tidal ventilation during sleep. Thus, no benefit for sleep has thus far been demonstrated in this population with rapidly declining VC.

Similar to those individuals with uncomplicated sleep-disordered breathing, ALS/MND patients, including those using DP,¹³ are sometimes prescribed CPAP or low-span bi-level PAP at inadequate settings to permit orthopedic patients to sleep supine or provide full ventilator support. A different strategy employs bi-level PAP at spans >15 cm H₂O, NIV at assist-control pressure cycling of ≥18 cm H₂O, or volume control at 800–1500 ml as full ventilator support settings to more completely rest inspiratory muscles during sleep and provide up to full support as it becomes necessary for prolonged tracheostomy-free survival.^{11,18,19}

Limitations to interpretation of our findings include that our study, and some of the earlier DP studies, could not distinguish ALS from predominantly lower MND.²⁰ Further, outcomes on only 8 ALS/MND patients cannot be generalized. The U.S. Food and Drug Administration approved DP placement for ALS on September 29, 2011 on the basis of its safety for humanitarian trials and not on the basis of efficacy.

In conclusion, in our study, DP was ineffective for 8 consecutive ALS/MND patients. Patients dependent on CNIV typically supplement autonomous tidal volumes by taking NIV via mouthpiece to avoid overtaxing the diaphragm. It may be that the DP user’s diaphragm, already working to capacity by autonomous production of tidal volumes that approach inspiratory capacity, has no physiologic neuromuscular reserve for DP to tap into and cannot decrease ventilator dependence. Considering the poor performance of DP, widespread public funding of DP systems in ALS may be premature and their use is unsupported by the current evidence.

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