

Interventional procedure overview of phrenic nerve pacing for ventilator-dependent high cervical spinal cord injury

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Table 1 Abbreviations

Abbreviation	Definition
ABD	Avery Biomedical Devices
ASIA	American Spinal Injury Association
CHS	Central hypoventilation syndrome
CCHS	Congenital central hypoventilation syndrome
ISCIQoLBDS	International spinal cord injury quality of life basic data set
IQR	Interquartile range
MV	Mechanical ventilation
PN	Phrenic nerve
PNP	Phrenic nerve pacing
RI	Respiratory tract infection
SCI	Spinal cord injury
SD	Standard deviation
SF-36	36-item short form health survey
SWLS	Satisfaction with life scale
VATS	Video assisted thoracoscopic surgery

Indications and current treatment

A high cervical SCI is an injury in the upper neck between the first and fourth cervical vertebrae (C1 to C4). SCIs can damage the PN that controls the diaphragm (the main muscle used in breathing) and cause chronic respiratory insufficiency. Some people with high cervical SCIs cannot breathe on their own, so they need a mechanical ventilator to help them breathe.

Standard care for managing respiratory insufficiency caused by SCIs includes non-invasive ventilation (such as bi-level positive airway pressure) and invasive

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MV (such as intubation or tracheostomy). An alternative to ventilatory support is intramuscular diaphragm stimulation for people with intact PN function.

Unmet need

People with respiratory insufficiency caused by SCIs need ventilatory support. While some people will remain ventilated after the treatment, many people with ventilator dependence may benefit from PNP. It offers some ventilator-free time, so reducing the risk of complications associated with MV and potentially improving quality of life.

What the procedure involves

This procedure involves directly stimulating the PN so that it sends a signal to the diaphragm to contract, which produces the inhalation phase of breathing. It aims to provide ventilatory support for people with intact PNs and functioning diaphragm muscles.

The procedure is usually done using a thoracic approach (often using a thoroscopic technique; thoracotomy is rarely used) and under general anaesthesia. Once the PN is identified and tested, an electrode is placed around the nerve in the chest, and then stabilised. The electrode is connected to a subcutaneous receiver, usually placed in the chest wall. An external transmitter (powered by batteries) then sends radiofrequency signals to the device through an antenna which is worn over the receiver. The receiver translates radio waves into stimulating electrical pulses that are delivered to the PN by the electrode, to achieve diaphragm contraction and support breathing. The device is tested during and after the surgery to ensure that it is working. This procedure is usually done bilaterally but can also be done unilaterally. A cervical approach can also be used and is done under general or local anaesthesia.

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After the procedure, the person follows a diaphragm conditioning programme, which involves progressive use of the system for increasing periods of time with gradual weaning from the ventilator.

Outcome measures

The main outcomes included survival, mode of ventilation, daily pacing duration, incidence of RI, quality of life, quality of speech, implant longevity, mortality, revision and PN damage. Some measures used (quality of life and quality of speech) are detailed in the following paragraphs.

The SF-36 questionnaire is an instrument for evaluating health-related quality of life. This questionnaire has 36 questions and covers 8 dimensions (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health), with scores for each dimension ranging from 0 to 100. Higher scores indicate higher health-related quality of life.

The SWLS is a short 5-item instrument designed to measure global cognitive judgements of satisfaction with one's life, with scores ranging from 5 to 35. Higher scores represent higher life satisfaction (5 to 9 indicating extremely dissatisfied; 31 to 35 representing extremely satisfied).

The ISCIQoLBDS reflects subjective quality of life. It consists of 3 variables: ratings of satisfaction with general quality of life, satisfaction with physical health, and satisfaction with psychological health. All variables are rated on a scale ranging from 0 (completely dissatisfied) to 10 (completely satisfied).

Quality of speech is measured on a scale ranging from 0 (no voice) to 6 (normal voice).

Evidence summary

Population and studies description

This interventional procedure overview is based on 1,647 people who had the procedure from 4 non-randomised comparative studies (Hirschfeld 2008, 2022; 2008; Romero 2012; Andersen 2017) and 1 analysis of the ABD database (Headley 2023). This is a rapid review of the literature, and a flow chart of the complete selection process is shown in [figure 1](#). This overview presents 5 studies as the key evidence in [table 2](#) and [table 3](#), and lists other relevant studies in [table 5](#).

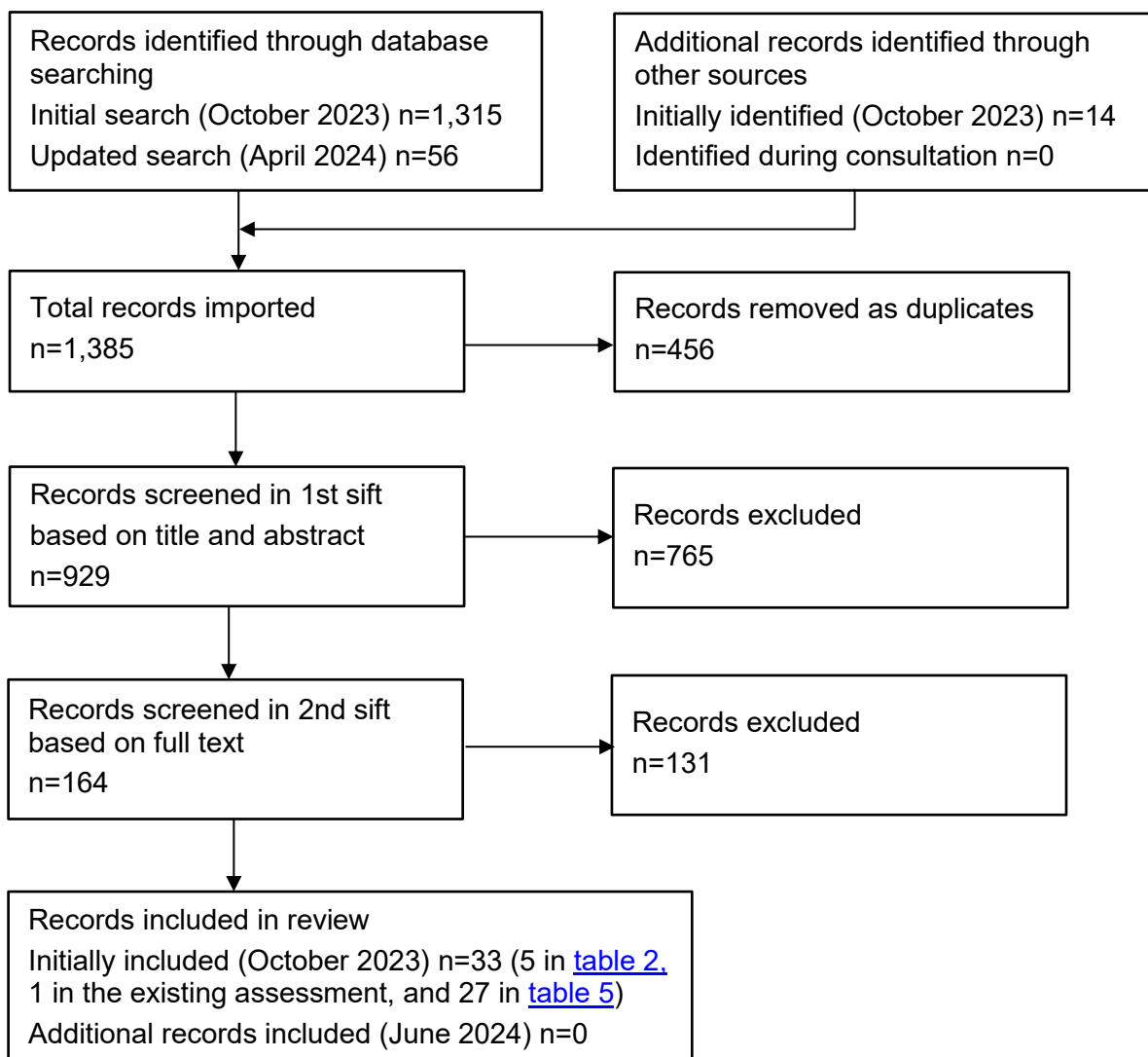
Of the 4 non-randomised comparative studies included in the key evidence, 2 studies (Hirschfeld 2022, 2008) were done in Germany, 1 study in Spain (Romero 2012), and 1 study in Denmark (Andersen 2017). There might be an overlap in the samples between Hirschfeld (2008) and Hirschfeld (2022).

These 4 studies included a total of 305 people who were ventilator-dependent caused by SCIs (n=303) and CHS (n=2). When reported, there were 222 people with traumatic SCIs and 58 people with non-traumatic SCIs (Hirschfeld 2008, 2023; Romero 2012). At baseline, age at injury was the main notable difference between people on PNP and those on MV. Hirschfeld (2022, 2008) and Romero (2012) noted that people on PNP were statistically significantly younger than those on MV. Although Andersen (2017) reported a younger age in the PNP group than the MV group, the difference was not statistically significant. There was no statistically significant difference in ASIA classification (Hirschfeld 2008; Romero 2012), but a statistically significant difference in SCI level between groups was noted in Romero (2012). The time interval from injury to PNP implantation was mean 21 months (Romero 2012) or median 1.47 years (Hirschfeld 2022). The follow up or observational period across 4 studies ranged from 10 to 33 years.

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The analysis of the ABD database (Headley 2023) included people with different indications (including SCIs) and potentially from different countries, but the exact number of people with ventilator-dependent high cervical SCIs was not reported. But it reviewed data collected over 38 years and included 1,522 people who had the Avery device implanted. Also, it particularly reported revision data and detailed the reasons for revisions (safety data). [Table 2](#) presents study details.

Figure 1 Flow chart of study selection



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Table 2 Study details

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Hirschfeld (2022) Germany (single centre)	92 (SCI, n=90; CHS, n=2) PNP, n=48 (31:17) MV, n=44 (34:10)	PNP, median 21 years; MV, median 27 years (p=0.001)	Non-randomised comparative study (prospective)	PNP: people with ventilator-dependent high tetraplegia caused by cervical SCI, intact PN, and people preference. MV: people on MV chosen as close as possible timely to those on PNP.	Bilateral PNP using Atrostim PN stimulator (Atrotech Ltd.) using a thoracic approach. MV (speaking valves)	33 years
2	Hirschfeld (2008) Germany (single centre)	64 (46:18) PNP, n=32 MV, n=32	PNP, median 29 years; MV, median 53 years	Non-randomised comparative study (prospective)	PNP: people with permanent respiratory device-dependence SCI, functional PN and diaphragm muscles, and people preference. MV: people with permanent	PNP using Atrostim PN stimulator (Atrotech Ltd.) Mobile MV	22 years

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Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
					respiratory device dependency and non-functioning PN.		
3	Romero (2012) Spain (single centre)	126 (88:38) PNP, n=38 MV, n=88	PNP, mean 17.8 years; MV, 45.5 years (p<0.001)	Non-randomised comparative study (retrospective analysis of prospectively collected data, with a follow-up quality-of-life questionnaire, by telephone or face-to-face)	People with respiratory failure because of diaphragmatic paralysis caused by high cervical SCI needing external respiratory support (either PNP or MV)	PN pacer (bipolar electrodes, n=6; 4-pole electrodes, n=32) implanted by open thoracotomy (n=31) or thoracoscopic technique (n=7). MV with a volumetric mechanical respirator.	Data reviewed: more than 10 years Questionnaire: cross-sectional
4	Andersen (2017) Denmark (2 sites)	23 (21:2) PNP, n=7 MV, n=16 (total 14 included in the analysis with 7 for each group)	PNP, median 26.7 years; people on MV, median 34.4 years; non-respondents on MV, median 49.5 years (p>0.05)	Non-randomised comparative study (retrospective with a follow-up questionnaire interview by telephone or during home visit)	PNP: tetraplegia caused by SCI with implanted PN pacer, aged 18 or over. MV: tetraplegia caused by SCI, active users of home MV constantly or some part of the	Bilateral PNP using Avery (n=4) and Atrotech (n=5) devices. MV: tracheostomy ventilation	Data reviewed: Up to 25 years Questionnaire: cross-sectional

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Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
					day, and aged 18 or over, with no mental health disorders.		
5	Headley (2023)	1,522 (including revision surgeries, a total of 3,478 devices implanted)	Mean 6.5 years (cervical, mean 6.4 years; thoracic, mean 6.4 years)	Analysis of the ABD database (retrospective)	People recorded in the ABD database over 38 years (1970 to 2008)	PN pacers initially implanted cervically (n=490), thoracically (n=583), or unknown locations (n=449)	Data reviewed: about 38 years
Studies 1 to 4 included (relatively) small samples, so had limited statistical power. Across these 4 studies, the key biases included: selection bias, bias due to confounding (age as a key confounder; age adjustment made by multiple logistic analysis [Cox regression] in Romero [2012]), and bias in measurement of outcomes. Romero (2012) was a retrospective analysis of prospectively collected data with a follow-up questionnaire. Anderson (2017) was retrospective in nature, with a follow-up questionnaire, and had reporting bias. Hirschfeld (2008, 2022) were prospective studies, but there might be an overlap in the samples. The key limitations for Headley (2023), included: retrospective in nature, a lack of baseline characteristics, bias in classification of intervention (because the database was only for the Avery device and other devices for the procedure existed), missing data, and mainly reported revision data across various indications, so a lack of other outcomes of interest (specifically for SCIs) reported.							

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Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Hirschfeld (2022)	Total sample, n=92 ventilator-dependent people (PNP, n=48; MV, n=44). Mode of ventilation: • PNP 24 hours (full-time use): n=30 • PNP intermittently (PNP during sleep): n=18 with 16 of them used MV during sleep for safety reasons For the 48 people on PNP, 36 people continued to use a tracheal cannula (speak valve), 9 had their tracheostoma plugged, and 3 had their tracheostoma closed. All 44 people on MV used speaking valves. RIs after discharge (RIs per 100 days; 0.274 per 100 days is equivalent to 1 RI per year): • PNP 24 hours (full-time use, n=30): 0.07 (SD, 0.17; range 0 to 0.9) • PNP intermittently (PNP during sleep, n=18): 0.08 (SD, 0.08; range 0 to 0.25) • MV (n=44): 0.2 (SD 0.15; range 0 to 0.78) The difference between MV and PNP is statistically significant, p=0.000. Survival for the whole group: 92.39% after 1 year, 63% after 10 years, and 60.9% after 20 years. A difference was in favour of PNP.	Mortality over 33 years: 40.2% (n=37; 19 PNP, 18 MV) Main causes: • Pneumonia: n=15 (1 PNP, 4 PNP and MV, 10 MV) • Intestinal occlusion: n=4 (2 PNP, 2 MV) • Decubital sepsis: n=2 (1 PNP, 1 MV) • Tumour and myelitis (PNP) • Heart failure: n=5 (4 PNP, 1 MV) • Suicide: n=3 (2 PNP, 1 MV) • Seizures: n=1 (PNP) • Bleeding: n=1 (PNP) • Non-specific SCI-induced: n=3 MV • Urosepsis (MV) PNP: n=13 (15 complications) • Within 3 weeks: 2 failing electrode sites and 5 haemo- or pneumothorax needed revisions. • Between 7 weeks and 5 years: 3 electrode sites needed revision, 1 of them 3 times; the latter nerve was lost, 1 dislocated stimulator

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First author, date	Efficacy outcomes	Safety outcomes
	Increasing age at injury correlated with decreasing survival, $p=0.009$. Age at injury had no influence on ASIA impairment scale type. Hospital stay: PNP, median 6.5 months; MV, median 9.5 months; $p=0.05$. With increasing age at injury, the duration of hospital stay increased, $p<0.05$ (Spearman's rho). Age at injury increased from motor lesion below C0 to below C3, $p=0.009$. Hospital stay for PNP only ($n=26$): median 26.3 days Frequencies differed for decubital ulcers (PNP 5, MV 18), $p=0.009$, and urological complications (PNP 13, MV 27), $p=0.037$. No significances were found for gastrointestinal complications (PNP 6, MV 8).	and 1 failing stimulator caused surgical intervention. 47% of all people developed granulomas in the tracheostoma; 22% needed surgical intervention, 1 person because of acquired tracheomalacia.
Hirschfeld (2008)	Total sample: $n=64$ who were permanently respiratory device-dependent (PNP, $n=32$; MV, $n=32$) Part-time use: all people needed their respiratory device during sleep. Total 10 people on PNP and 4 on MV used their device part time. Survival: PNP, $n=20$ (63%); MV, $n=18$ (56%) A trend was in favour of PNP, but the difference compared with MV was not statistically significant (log-rank $p=0.184$). Incidence of IRs: PNP compared with MV, median (IQR), IRs per 100 days: Period 1 (defined by the study as 120 days in institution before using the final respiratory device): 1.43 (0.05 to 3.92) compared with 1.33 (0.89 to 2.21); $p=0.888$	Mortality: PNP, $n=12$; MV, $n=14$; $p=0.1023$ Death caused by RI: PNP, $n=3$; MV, $n=10$; $p=0.0472$

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First author, date	Efficacy outcomes	Safety outcomes
	- Period 2 (defined by the study as from beginning of use of final device until leave from institution for final location): 0 (0 to 0.92) compared with 2.07 (1.49 to 4.19); $p < 0.001$ - Period 3 (defined by the study as after arrival at final location, covers total time of follow up, at least 1 year): 0 (0 to 0.02) to 0.14 (0 to 0.31); $p < 0.001$ Statistically significant differences between periods 1 and 2, and periods 2 and 3 for each group Status of life (PNP, n=20; MV, n=18) - Return to school: PNP, n=7; MV, n=2 - Return to work: PNP, n=2; MV, n=0 - Retired: PNP, n=11; MV, n=16 The trend in favour of PNP was because of age, not because of the type of respiratory treatment. Quality of speech: significantly better with PNP (the lowest score was 3 (median 6 [5.25 to 6]), than with MV, where speech scores were frequently 1 and 2 (median 3.5 [2 to 5.75]), $p < 0.001$. Ability to talk: no difference between groups (exact data not reported) Feedback from people: people and their doctors found the quality of life better with PNP than with MV. People on PNP showed more self-confidence and no one using PNP wanted to return to MV. People on MV frequently regretted that PNP was not suitable for them.	
Romero (2012)	Total sample: n=126 (PNP, n=38; MV, n=88)	Mortality:

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First author, date	Efficacy outcomes	Safety outcomes
	Mode of ventilation in the 27 people alive at time of reporting in the PNP group: • PNP: n=20 • PNP (mainstay) and volumetric respirator (during nighttime sleep): n=5 • Moved to MV: n=2 during follow ups at 11.25 and 15.74 years (the first because of infection of the implanted device and the second because of severe deterioration of PN conduction) Survival: PNP, n=28 (74%); MV, n=39 (44%); p=0.003 Note: there was a discrepancy in the reported number of people alive on PNP. Survival expectancy in years: PNP, 21.78 (95% CI, 17.95 to 25.61); MV, 8.69 (95% CI, 6.37 to 11.02); p<0.001 Multiple logistic analysis (Cox regression): After age was adjusted, the length of survival was greater for people with PNP (p=0.04). SF-36 questionnaire (n=36): • Total score: PNP, 81.29 (SD 13.82); MV, 82.80 (SD 16.28); p=0.56 • Social functioning: PNP, 7.67 (SD 1.80); MV, 5.67 (SD 1.17); p<0.001 • Other domains: all p>0.05	• PNP, n=11 (respiratory causes, n=6; other causes, n=4) The study also reported death in 10 people so there was a discrepancy in reporting. • MV, n=49 (respiratory causes, n=41; other causes, n=8) Infection of the implanted device from a wire that was inside a pressure ulcer: n=1, the person moved from PNP to MV PN degeneration: n=1, the person moved from PNP to MV
Andersen (2017)	Total sample: n=23 (PNP, n=7; MV, n=16, with 7 included in the analysis)	Not reported

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First author, date	Efficacy outcomes	Safety outcomes
	Daily pacing hours: 8.5 to 16 hours per day (8.5 hours, n=1; 12 to 14 hours, n=3; 16 hours, n=3) Length of pacing: 1.5 years to 25.4 years Patient experience of using pacer: median 6 (range 5 to 7) on a scale of 1 (most possible trouble making the pacer work) to 7 (no problems at all). Comparison between PNP (n=7) and MV (n=7), median (range): • Quality of speech: 5 (4 to 6) compared with 5 (5 to 6) • Number of pneumonias within last year: 0 (0 to 3) compared with 0 (0 to 2) • Hospitalisations for pneumonia within last year: 0 (0 to 2) compared with 0 (0 to 1) • Number of daily suction: 3 (0 to 12) compared with 1 (0 to 5) No statistically significant differences were found between groups. Quality of life comparison between PNP (n=7) and MV (n=7), median (range): • SWLS: 21 (7 to 28) compared with 19 (11 to 28) • ISCIQoLBDS – general: 7 (0 to 9) compared with 7 (3 to 9) • ISCIQoLBDS – physical: 7 (0 to 9) compared with 6 (2 to 8) • ISCIQoLBDS – mental: 7 (5 to 10) compared with 8 (2 to 10) • SF36 physical summary: 35.4 (12.9 to 37.6) compared with 23.6 (14 to 37.6)	

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First author, date	Efficacy outcomes	Safety outcomes
	SF36 mental summary: 62.3 (51.1 to 71.2) to 61.4 (27 to 71.4) No statistically significant differences were found between 2 groups or with the US norm data. After the SCI only 1 person on PNP completed an education. One person on MV was completing their education and another was taking some occasional educational courses.	
Headley (2023)	Total sample: n=1,522 (3,478 devices implanted) Years spent pacing: Pacing for over 40 years: n=3 alive at time of reporting; n=2 deceased at time of reporting Pacing for over 30 years: n=33 alive at time of reporting; n=8 deceased at time of reporting Longevity of implants: 6.5 years (median, 5; SD 6.2) no significant difference in the amount of time implants last between approaches: cervical (mean 6.4 years; SD 6.8) and thoracic (mean 6.4 years; SD 5.7) (p=0.9382). Survey results (n=111): - Tracheostomy removal: 76% of respondents had a tracheostomy before implantation, and of these, about 33% chose to have them removed following implantation. - Patient-reported daily amount of time spent pacing: 7 to 12 hours daily: 57% of respondents, primarily while sleeping (common diagnoses: central sleep apnoea and CCHS). 13 to 15 hours daily: 14% of respondents	Revision surgeries for the I-110 receiver (current version): n=172 of 854 people with the I-110 receiver implant. Electrode revision: 169 out of 962 people (47 with unknown location) needed revision, with a total of 209 revisions (change location, n=47) - people with cervical approach: 66 out of 380 people (17%) needed revision, with a total of 82 revisions (change cervical to thoracic location, n=37 [45%]; no change to location, n=25) - people with thoracic approach: 95 out of 518 people (18%) needed revision, with a total of 113 revisions (change thoracic to cervical location, n=10 [10%]; no change to location, n=77) - people with 1 side cervical and 1 side thoracic implantation: 7 out of 9 people needed revision, with a total of 14 revisions

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First author, date	Efficacy outcomes	Safety outcomes
	○ 16 to 20 hours daily: 13% of respondents ○ 24 hours a day: 16% of respondents	Reasons for revision for cervically implanted PN pacers: • no report or no problem found: 18% • surgical placement of implants: 14% • intermittent (loss of stimulation): 14% • insulation damage: 12% • damage to wire: 9% • calcification of anode: 8% • accidental damage (sports): 6% • accidental damage (medical treatment): 5% • infection after surgery: 5% • people who play or fidget with their subcutaneously placed receivers: 4% • patient growth: 5% PN damage: n=6 (of 3,478 implants; less than 0.2%) caused by surgical manipulation of the nerve. One of these cases happened using the cervically implanted electrode. In 5 of the 6 cases the nerve function recovered.

Procedure technique

All 4 non-randomised comparative studies described the procedure technique but varied in detail. Two devices (Avery and Atrotech) were used.

The function of PN and diaphragm muscles was ascertained by neurophysiologic and fluoroscopic or sonographic studies (Hirschfeld 2008). This was done by applying external current to the nerve transcutaneously on the neck, while measuring diaphragm contraction with fluoroscopy or ultrasound (Andersen 2017).

When reported, both bipolar and 4-pole electrodes were used, with the latter used more frequently. The common approach to implantation was by an open thoracotomy, with the minority using a thoracoscopic technique. The procedure was usually done bilaterally.

After the procedure, the mean conditioning duration was 47 days (Romero 2012) to 50 days (Hirschfeld 2022).

For the review of the ABD database, Headley (2023) generally described the procedure technique with a cervical or thoracic approach. The authors stated that positive identification of the PN was achieved with a disposable nerve stimulator revealing diaphragm movement. The cervical technique remained the most minimally invasive technique and could be done under local anaesthesia. But, there was a greater area of accessible PN in the chest for placement of the electrode, so more thoracic surgeons have been practicing thoracic placement (using either the open thoracostomy or the less invasive VATS technique) as opposed to cervical placement. Also, thoracic placement of the electrodes was more common in children.

Efficacy

Survival

Survival data was reported in 3 studies, with a tendency towards better survival with PNP than with MV. Hirschfeld (2022) reported that, for the whole study population of 92 people, the survival rate was 92% after 1 year, 63% after 10 years, and 61% after 20 years. A difference was in favour of PNP. People on PNP were younger than those on MV ($p=0.001$) at injury and increasing age at injury correlated with decreasing survival ($p=0.009$).

Hirschfeld (2008) found that the survival rate was 63% (20 of 32) in people on PNP and 56% (18 of 32) in people on MV over 22 years. A trend was in favour of PNP, but the difference compared with MV was not statistically significant (log-rank $p=0.184$).

Romero (2012) described that the survival rate was 74% (28 of 38) in people on PNP and 44% (39 of 88) in people on MV over 10 years. The length of survival was statistically significantly longer in the PNP group than the MV group (PNP, 21.78 years; MV, 8.69 years; $p<0.001$). Once age was adjusted, the length of survival was greater for people on PNP than those on MV ($p=0.04$).

Mode of ventilation or daily pacing duration

Mode of ventilation or daily pacing hours were reported in 4 studies. PNP represented the weaning from MV at various levels, with 25% to 74% of people using PNP as their only mode of ventilation and the daily pacing duration between 7 and 24 hours.

Hirschfeld (2022) reported that of the 92 ventilator-dependent people, 48 people were on PNP and 44 were on MV. For the PNP group, 63% (30 of 48) of people used PNP full time (24 hours) and 38% (18 of 48) of people used PNP intermittently (with 16 of them using MV during sleep for safety reasons). For the

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48 people on PNP, 75% (36 of 48) of people continued to use a tracheal cannula, 19% (9 of 48) had their tracheostoma plugged, and 6% (3 of 48) had the tracheostoma closed.

Hirschfeld (2008) found that all 64 people (32 on PNP and 32 on MV) needed their respiratory devices during sleep. Ten people on PNP and 4 on MV used their device part time, so they could use glossopharyngeal breathing or their accessory respiratory muscles in the neck intermittently. This facilitates nursing and improves the chance to survive respiratory device failure.

Romero (2012) reported that, of the 38 people on PNP who needed permanent MV before the procedure, 27 people survived over 10 years after implantation. Of these people, 74% (20 of 27) people used PNP as their only mode of ventilation, 19% (5 of 27) used a mixed model (PNP as the main mode and MV during sleep hours), and 7% (2 of 27) moved to MV (1 had the PNP explanted because of infection and the other could no longer use it because of PN degeneration).

In the Anderson (2017) study of 14 ventilator-dependent people, 7 people had a PN pacer implanted. Their daily pacing duration was 8.5 hours in 1 person, 12 to 14 hours in 3 people and 16 hours in 3 people. This was in line with the recommendation from the study site's respiratory centre that the pacer should not be used for more than 16 hours per day to prevent any damage to the PN. The total period of pacing ranged from 1.5 years to 25.4 years.

In the analysis of the ABD database, Headley (2023) reported that, of the 111 people who responded to the survey, 57% of respondents reported that they paced for 7 to 12 hours daily, primarily while sleeping, 14% reported 13 to 15 hours daily, 13% reported 16 to 20 hours daily, and 16% used the pacer at all times. The authors also found that 5 people were pacing for 40 years (2 of these people were reported as now deceased in the database), and 41 people were pacing for over 30 years (8 of these people were reported as now deceased).

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The survey results also showed that 76% of respondents had a tracheostomy before implantation, and of these people, around 33% chose to have it removed following implantation.

Incidence of RIs

RI was recorded when the person presented with fever, leucocytosis, increased production of secretions and the doctor in charge diagnosed the reason to be RI with antimicrobial treatment being necessary. The data on the incidence of RIs or pneumonias was reported in 3 studies. There were statistically significant reductions in the incidence of RIs after implantation and fewer RIs in the PNP group than the MV group. This difference was not found for pneumonia.

Hirschfeld (2022) reported that the incidence of RIs after discharge was statistically significantly lower in people using PNP (30 people on PNP for 24 hours a day, 0.07 RIs per 100 days; 18 people on PNP intermittently, 0.08 RIs per 100 days) than people using MV (n=44, 0.2 RIs per 100 days; $p=0.000$).

Hirschfeld (2008) reported incidence of RIs in 3 periods: period 1 (reported as 120 days in institution before using final respiratory device); period 2 (reported as from beginning of use of final device until leave from institution for final location) and period 3 (reported as after arrival at final location, including total time of follow up, at least 1 year). There was no significant difference in the median incidence of RIs between the PNP group (n=32) and the MV group (n=32) in period 1. But, during post-implantation (period 2 and period 3) there were statistically significantly fewer RIs in the PNP group than the MV group:

- Period 1: 1.43 RIs per 100 days (IQR 0.05 to 3.92) compared with 1.33 RIs per 100 days (IQR 0.89 to 2.21); $p=0.888$.
- Period 2: 0 RI per 100 days (IQR 0 to 0.92) compared with 2.07 RIs per 100 days (IQR 1.49 to 4.19); $p<0.001$.

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- Period 3: 0 RI per 100 days (IQR 0.00 to 0.02) compared with 0.14 RIs per 100 days (IQR 0.00 to 0.31); $p < 0.001$.

The authors also found that there were statistically significant reductions in RI incidence between periods 1 and 2, and periods 2 and 3 for each group.

Anderson (2017) found no statistically significant differences between people on PNP ($n=7$) and people on MV ($n=7$) in the number of pneumonias within the last year (median 0 compared with 0), hospitalisations for pneumonias within the last year (median 0 compared with 0), and number of daily suction (median 3 compared with 1).

Quality of life and return to productivity

Quality of life was reported in 2 studies and various measures were used. When comparing PNP with MV, there was no statistically significant difference in quality of life across studies, except that SF-36 social functioning improved significantly in 1 study.

Romero (2012) reported that, of the 126 people, 44 people completed the SF-36 questionnaire (24 on PNP and 20 on MV). To avoid selection bias, 36 people with C1 to C2 level ASIA A grade of SCI were included in this analysis. The results showed that people on PNP had a statistically significantly higher score in the social functioning dimension ($p=0.0002$) than people on MV, but no statistically significant differences in other domains or in the total scores (all $p > 0.05$).

Andersen (2017) did not find any significant differences in SWLS, ISCIQoLBDS (general, physical and mental domains) and SF-36 (physical and mental domains) scores between the PNP group ($n=7$) and the MV group ($n=7$).

In terms of return to productivity, the data was described in 2 studies and age might play an important role in this outcome. Hirschfeld (2008) reported that of 64 people, 38 people (20 on PNP and 18 on MV) lived at home at the end of the IP overview: phrenic nerve pacing for ventilator-dependent high cervical spinal cord injury

study. Of these 38 people, 7 people on PNP and 2 on MV returned to school, 2 people on PNP but none on MV returned to work and all others retired.

Anderson (2017) reported that of the 14 people, after their SCI, only 1 person on PNP completed education. One person on MV was completing their education and another was taking some occasional educational courses.

Quality of speech

Quality of speech was evaluated in 2 studies with mixed outcomes. With pressure-controlled MV, people talk during inspiration; with PNP, people talk during expiration. Hirschfeld (2008) reported that the quality of speech was statistically significantly better in people with PNP (median score 6 [normal voice]), than people with MV (median score 3.5 [between intermittently low voice and low voice], $p < 0.001$). But there was no difference between groups in the ability to talk (exact data not reported). Anderson (2017) found no statistically significant difference in the quality of speech between the PNP group and the MV group (median score 5 [intermittently normal voice] for each group).

Implant longevity

Implant longevity was indicated by years in between revision surgeries and presented in the Headley (2023) study. The authors reviewed the ABD database of 1,522 people and found that the mean longevity was 6.5 years (SD 6.2) for both cervical and thoracic approaches. When comparing 2 approaches, there was no statistically significant difference in device longevity (cervically implanted device: mean 6.4 years, SD 6.8; thoracically implanted: mean 6.4 years, SD 5.7; $p = 0.9382$).

Safety

Mortality and causes

Mortality and its causes were described in 3 studies and the mortality rate ranged from 29% to 40% in people on PNP. Hirschfeld (2022) reported that, of 92 people, 37 people (PNP, n=19 [40%]; MV, n=18 [41%]) died over a 33-year time period. The leading cause was pneumonia (4 PNP and MV, 1 PNP used for 24 hours a day, and 10 MV). The other reasons were non-specific SCI-induced (3 MV), intestinal occlusion (2 PNP, 2 MV), decubital sepsis (1 PNP, 1 MV), urosepsis (MV), tumour and myelitis (PNP), heart failure (4 PNP and 1 MV), suicide (2 PNP and 1 MV), seizures (1 PNP) and bleeding (1 PNP).

Hirschfeld (2008) reported that 12 people (38%) on PNP and 14 people (44%) on MV died over a 22-year time period ($p=0.1023$); of these people, 3 on PNP and 10 on MV died of RIs ($p=0.0472$).

Romero (2012) reported that the mortality rate was 29% (11 of 38) for people on PNP and 56% (49 of 88) for people on MV over 10 years. Most died from respiratory causes.

Revision and causes

Headley (2023) reported that, of 854 people who had the current version of the receiver implanted (version I-110), 20% (172 of 854) needed revision surgeries. For the electrodes, 17% (66 of 380) of cervical cases needed at least 1 revision of the electrode compared with 18% (95 of 518) of thoracic cases. Data showed that in people who initially had implanted cervically, 45% of electrode revisions involved moving the electrode placement to the chest compared with 10% of people whose implants were moved from the chest to the neck. The authors also reported the revision rationale for people with cervical implantation as follows:

- no report or no problem found: 18%

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- surgical placement of implants: 14%
- intermittent (loss of stimulation): 14%
- insulation damage: 12%
- damage to wire: 9%
- calcification of anode: 8%
- accidental damage (sports): 6%
- accidental damage (medical treatment): 5%
- infection after surgery: 5%
- people who play or fidget with their subcutaneously placed receivers: 4%
- patient growth: 5%.

Hirschfeld (2022) reported that within 5 years of the procedure, there were 15 complications needing revisions in 13 people (27%) because of bilateral PN pacer implantation. These included failing electrode sites (n=2), haemothorax or pneumothorax (n=5), nerve loss (n=1), dislocated stimulator (n=1) and failing stimulator (n=1).

PN damage

PN damage was reported in 2 studies. Headley (2023) found that, of the 3,478 implants, PN injury caused by surgical manipulation of the nerve was reported in 6 cases over 38 years (less than 0.2%). In 5 of the 6 cases the nerve function recovered. Hirschfeld (2022) reported that, of the 92 people, the rate of nerves at risk was 4% (7.3 of 184) and 1 nerve (0.5%) was lost.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if

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they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal or theoretical adverse events: malfunctioning of the device needing replacement, respiratory failure, bleeding, infection and injury to chest organs.

Two professional expert questionnaires for this procedure were submitted. Find full details of what the professional expert said about the procedure in the [specialist advice questionnaires for this procedure](#).

Validity and generalisability

Of the 4 non-randomised comparative studies, 2 studies were prospective, 1 study was a retrospective analysis of prospectively collected data with a follow-up questionnaire, and 1 study was retrospective with a follow-up questionnaire in design. The sample size ranged from 23 to 92 people across these 4 studies. When considering the number of people with SCIs who used PNP, the sample size ranged from 7 to 46 people. The follow-up or observational period was between 10 and 33 years after implantation.

For the review of the ABD database, Headley (2023) included a large sample with mixed indications, but the exact number of people with ventilator-dependent high cervical SCIs was unknown. This review mainly focused on the revision aspect, so there was a lack of other outcomes of interest reported.

Across all studies, only 1 paper's authors declared their conflicts of interest (Headley 2023), while other papers did not report conflicts of interest. None of the studies were funded by manufacturers.

Overall, the evidence suggests a tendency towards better survival with PNP than with MV. This might be due to younger age rather than the type of respiratory treatment and people on PNP were generally younger than those on MV

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(Hirschfeld 2022). Younger age (being more active) could also be 1 of the reasons for better return to productivity with PNP than with MV (Hirschfeld 2008).

PNP represented the weaning from MV at various levels and the longest length of pacing was over 40 years. There were statistically significant reductions in the incidence of RIs after implantation and fewer RIs in the PNP group than the MV group but not for pneumonia.

Regarding quality of life, when comparing PNP with MV, there were no statistically significant differences across studies, except that SF-36 social functioning improved significantly in 1 study. This improvement might be due to people's preference for PNP with improved portability, without tubes and with low maintenance requirements (Hirschfeld 2022; Romero 2012). However, the SF-36 questionnaire was not an ideal measurement for people with SCIs, in particular 'nominated physical functioning' (Romero 2012). Also, the quality of speech was assessed, demonstrating mixed outcomes, and no validated tool was available.

Implant longevity was measured by years in between revision surgeries, with the mean longevity being 6.5 years. The data on revision mainly came from a review of the ABD database, indicating that the rate of revision surgeries for the I-110 receiver (current version) was 20%. The rate of mortality ranged from 29% to 40% in people with PNP, with the leading cause being RIs. Other complications, such as PN damage, were rare.

In conclusion, the evidence shows improvements in outcomes. Although some improvements were limited, these limited improvements must be interpreted in the context of people with high cervical SCI who have multiple comorbidities and this procedure is to treat 1 component of a very complex condition. To date, no ongoing trials have been identified.

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Existing assessments of this procedure

In April 2013, the NHS Commissioning Board (CB) published the clinical commissioning policy on PNP following SCI (NHS Commissioning Board Clinical Reference Group, 2013). The NHS CB states that the specialist nature of this intervention and the fact that only 1 UK centre has published outcome data imply that, should it be commissioned, this procedure may only be suitable for provision in designated centres with special arrangements for clinical governance, consent, and audit or research.

The NHS Commissioning Board will commission PNP following SCI in accordance with the criteria for selecting people with chronic ventilator-dependent traumatic or non-traumatic SCIs:

- Who have been offered the opportunity to discuss the clinical and psychological impact of the 2 possible outcomes of assessment and their responses to receiving a positive or negative screening outcome. This should be undertaken by suitable trained consultants in SCI and respiratory management after SCI, and a SCI clinical psychologist.
- Who have an intact functioning PN, as confirmed by electromyographic response of the diaphragm to nerve stimulation.
- Who have discussed with the implanting consultant the known risks and benefits associated with surgery and implantation and given their consent for surgery.
- Who are under the care of the commissioned implanting centre.

Related NICE guidance

Interventional procedures

- [NICE interventional procedures guidance on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure from high spinal](#)

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[cord injuries](#) (published 24 May 2023; recommendation: special arrangements).

- [NICE interventional procedures guidance on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease](#) (published 27 September 2017; recommendation: do not use).

NICE guidelines

- [NICE guideline on rehabilitation after traumatic injury](#) (published 18 January 2022).

Professional societies

- Association of British Neurologists
- Society of British Neurological Surgeons
- British Association of Spinal Cord Injury Specialists
- British Association of Spinal Surgeons
- British Thoracic Society
- Faculty of Intensive Care Medicine
- Intensive Care Society.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

1. Hirschfeld S, Huhtala H, Thietje R et al. (2022) Phrenic nerve stimulation experiences. A single centre, controlled, prospective study. Journal of IP overview: phrenic nerve pacing for ventilator-dependent high cervical spinal cord injury

clinical neuroscience: official journal of the Neurosurgical Society of Australasia 101: 26-31

2. Hirschfeld S, Exner G, Luukkaala T et al. (2008) Mechanical ventilation or phrenic nerve stimulation for treatment of spinal cord injury-induced respiratory insufficiency. *Spinal cord* 46(11): 738-42
3. Romero FJ, Gambarrutta C, Garcia-Forcada A et al. (2012) Long-term evaluation of phrenic nerve pacing for respiratory failure due to high cervical spinal cord injury. *Spinal cord* 50(12): 895-8
4. Andersen MP, Laub M, Biering-Sorensen F (2017) Phrenic pacing compared with mechanical ventilation. *Spinal cord series and cases* 3: 17022
5. Headley DB, Martins AG, McShane KJ et al. (2023) Diaphragm pacing using the minimally invasive cervical approach. *The journal of spinal cord medicine* 46(1): 26-34
6. The NHS Commissioning Board Clinical Reference Group (2013) [Clinical Commissioning Policy: Phrenic Nerve Pacing Following Spinal Cord Injury](#). Accessed 24 November 2023

Methods

NICE identified studies and reviews relevant to PNP for ventilator-dependent high cervical SCI from the medical literature. The following databases were searched between the date they started to 18 April 2024: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the [literature search strategy](#)). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also

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excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events not available in the published literature.

- People with high cervical SCI with ventilator dependency.
- Intervention or test: PNP.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on [other relevant studies](#).

Find out more about [how NICE selects the evidence for the committee](#).

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE ALL (Ovid)	18/04/2024	1946 to April 17, 2024
EMBASE (Ovid)	18/04/2024	1974 to April 17 2024
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	18/04/2024	Issue 4 of 12, April 2024
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	18/04/2024	Issue 3 of 12, March 2024
International HTA database (INAHTA)	18/04/2024	-

Trial sources searched:

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry.

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Websites searched:

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search.

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

- 1 Phrenic Nerve/
- 2 Diaphragm/
- 3 1 or 2
- 4 (pacing or stimulat*).tw.
- 5 3 and 4
- 6 ((phrenic nerve* or diaphragm*) adj4 (pacing or stimulat*)).tw.
- 7 5 or 6
- 8 ((Congenital adj2 central adj2 hypoventilation adj2 syndrome*) or CCHS).tw.
- 9 (Primary adj2 central adj2 hypoventilation adj2 syndrome*).tw.
- 10 (Central adj4 hypoventilation).tw.
- 11 "Ondine's curse".tw.
- 12 or/8-11
- 13 Spinal Cord Injuries/
- 14 ((Spinal adj4 cord adj4 (injur* or trauma* or contusion* or lacerat*)) or SCI).tw.
- 15 Respiration, Artificial/
- 16 (((artificial or mechanical) adj4 ventilat*) or (Ventilat* adj4 dependen*)).tw.
- 17 Respiratory Insufficiency/
- 18 (Respiratory adj4 (failure* or artificial or Insufficien* or depression)).tw.
- 19 or/13-18
- 20 12 or 19
- 21 7 and 20
- 22 (Avery adj4 Diaphragm adj4 (Pace* or pacing)).tw.

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23 ((Atrostim or atrotech) adj4 (Phrenic adj4 Nerve)).tw.
24 21 or 22 or 23
25 Animals/ not Humans/
26 24 not 25
27 limit 26 to english language

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Baer GA, Talonen PP, Shneerson JM et al. (1990) Phrenic nerve stimulation for central ventilatory failure with bipolar and four-pole electrode systems. Pacing and clinical electrophysiology: PACE 13(8): 1061-72	Case series n=10 (C2-tetraplegia, n=7; central sleep apnoea, n=3)	Diaphragmatic pacing may enable people who are tetraplegic to become completely independent of mechanical ventilators, and thereby be able to enter rehabilitation centres for people with SCIs. In selected people it is a valuable method of treatment that is not often considered, sequential four-pole stimulation of the PN seems to give clinical results no worse than those with unipolar diaphragm pacing.	Small sample; more recent studies included
Bolikal P, Bach JR and Goncalves M (2012) Electrophrenic pacing and decannulation for high-level spinal cord injury: a case series. The journal of spinal cord medicine 35(3): 170-4	Case series n=4	Lack of ventilator-free breathing ability in people with high-level SCI does not mandate tracheostomy, or electrophrenic or diaphragm pacing.	Small sample
Campbell DA, Homan SD, McCulloch GA et al. (1992) Phrenic	Case series n=2	PNP to achieve full-time or partial ventilator independence should be considered in people of all	Small sample; more recent studies included

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nerve pacing in two young quadriplegic ventilator-dependent patients. Australian and New Zealand journal of medicine 22(5): 463-8		ages with high SCI as a means of improving quality of life and as a part of rehabilitation to achieve independence in the community.	
DiMarco AF, Takaoka Y and Kowalski KE (2005) Combined intercostal and diaphragm pacing to provide artificial ventilation in patients with tetraplegia. Archives of physical medicine and rehabilitation 86(6): 1200-7	Prospective single-arm trial (case series) n=4 follow up: 1 year?	Combined intercostal and unilateral diaphragm pacing may be a useful therapeutic modality capable of maintaining long-term ventilatory support in people with only unilateral PN function.	Small sample and combined intercostal and diaphragm pacing
Elefteriades JA, Quin JA, Hogan JF et al. (2002) Long-term follow-up of pacing of the conditioned diaphragm in quadriplegia. Pacing and clinical electrophysiology: PACE 25(6): 897-906	Case series (retrospective) n=12 follow up: 8.8 years	This follow up confirms that people who are quadriplegic are able to meet long-term, full-time ventilation requirements using PN stimulation of the conditioned diaphragm. Careful review of diaphragmatic pacing candidates with respect to associated medical conditions, social support, and motivation is essential for appropriate patient selection and successful long-term results.	Small sample; more recent studies included
Fodstad H (1989) Pacing of the diaphragm to control breathing in patients with paralysis of central nervous system origin. Stereotactic and functional	Case series n=35 follow up: mean 46 months	At a mean follow-up time of 46 months, 15 people are entirely independent of respirator and 8 people with quadriplegia ventilate with pacers at different daytime intervals and use MV during the night. Five people have stopped pacing and 7	Mixed indications and outcomes for SCI not reported separately. More recent studies included

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neurosurgery 53(4): 209-22		additional people have died of causes unrelated to electrophrenic stimulation.	
Garrido-Garcia H, Mazaira Alvarez J, Martin Escribano P et al. (1998) Treatment of chronic ventilatory failure using a diaphragmatic pacemaker. Spinal cord 36(5): 310-4	Case series n=22	Evidence shows that complete stable ventilation can be achieved using diaphragmatic pacing and that it improves the prognosis and life quality of people with severe chronic respiratory failure.	Mixed indications and outcomes for SCI not reported separately. More recent studies included
Glenn WWL, Brouillete RT, Dentz B et al. (1988) Fundamental considerations in pacing of the diaphragm for chronic ventilatory insufficiency: a multi-centre study. PACE, 11: 2121-7	Case series (retrospective) n=475 (SCI, n=169)	Key recommendations: 1. A programme to assure long-term follow-up of people by physicians and paramedical personnel knowledgeable in pacing; 2. Facilities for regular monitoring of pacemaker performance and people's response to pacing; 3. Improved techniques of pacing the diaphragm, particularly the development of state-of-the-art neural stimulators; 4. Autopsy examination of all deceased people who have had a diaphragm pacemaker implanted, with detailed study of the PN and diaphragm muscle to determine the effects of electrical stimulation on these vital structures: Pathological studies will provide definitive factual information required to determine the future role of diaphragm pacing in the treatment of chronic ventilatory insufficiency and which will be applicable to	Mixed indications and key outcomes for SCI not reported separately. More recent studies included

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		other neuromuscular stimulation.	
Khong P, Lazzaro A and Mobbs R (2010) Phrenic nerve stimulation: the Australian experience. Journal of clinical neuroscience 17: 205-8	Case series (retrospective) n=19 follow up: 1 to 21 years	The data suggests that PN stimulation can be used instead of mechanical ventilators for long-term ongoing respiratory support.	Mixed indications and outcomes for SCI not reported separately
Hunt CE, Brouillette RT, Weese-Mayer DE et al. (1988) Diaphragm pacing in infants and children. Pacing and clinical electrophysiology: PACE 11(11pt2): 2135-41	Case series n=34	Regardless of outcome of the efforts to achieve continuous long-term pacing, pacing is already an effective treatment in infants and young children, eliminating the need for positive pressure ventilation when awake breathing is normal and substantially improving quality of life in children requiring awake ventilatory support.	Small sample; more recent studies included
Kaufman MR, Bauer T, Campbell S et al. (2022) Prospective analysis of a surgical algorithm to achieve ventilator weaning in cervical tetraplegia. The journal of spinal cord medicine 45(4): 531-5	Case series n=10	Although more investigation is necessary, PN reconstruction or diaphragm muscle replacement performed (when indicated) with pacemaker implantation may allow virtually all ventilator-dependent cervical people with tetraplegia to partially or completely wean.	Small sample, with most people having combined PNP with other procedures
Kaufman MR, Elkwood AJ, Aboharb F et al. (2015) Diaphragmatic reinnervation in ventilator-dependent patients with cervical spinal cord injury and	Case series (retrospective) n=14	Simultaneous nerve transfers and pacemaker implantation can result in reinnervation of the diaphragm and lead to successful ventilator weaning. The favourable outcomes support consideration of this surgical method for	Small sample and combined nerve transfer and PNP

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concomitant phrenic nerve lesions using simultaneous nerve transfers and implantable neurostimulators. Journal of reconstructive microsurgery 31(5): 391-5		appropriate people who would otherwise have no alternative therapy to achieve sustained periods of ventilator independence.	
Krieger LM and Krieger AJ (2000) The intercostal to phrenic nerve transfer: an effective means of reanimating the diaphragm in patients with high cervical spine injury. Plastic and reconstructive surgery 105(4): 1255-61	Case series n=6	Intercostal to PN transfer with diaphragmatic pacing is a viable means of liberating people with high SCI from long-term MV.	Small sample and combined technique of nerve transfer and PNP; more recent studies included
Krishnan U, Ramrakha PS and Money-Kyrle A (2010) A rare instance of 'cardio-respiratory pacing': permanent pacemaker insertion for symptomatic bradycardia in a quadriplegic man dependent on diaphragmatic pacing by phrenic nerve stimulators. Cardiology 116(2): 98-100	Case report n=1	This paper describes a person who required cardiac pacemaker insertion in the presence of PN stimulators for ventilator support. This is the first reported instance of the successful combination of cardiac and respiratory pacemakers without electromagnetic interference.	Single case report
Lam JCM, Ho CTK, Poon TL et al. (2009) Implantation of a breathing pacemaker in a	Case report n=1	Use of a diaphragm pacing stimulation system is a viable alternative to MV in people with tetraplegia with chronic respiratory	Small sample

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tetraplegic patient in Hong Kong. Hong Kong medical journal = Xianggang yi xue za zhi 15(3): 230-3		insufficiency. Implantation of the diaphragm pacers in appropriate subjects can lead to independent living, enhanced mobility, better quality of life, and ease their integration into society. A multidisciplinary team approach is crucial for achieving a successful outcome.	
Layachi L, Georges M, Gonzalez-Bermejo J et al. (2015) Diaphragm pacing failure secondary to deteriorated chest wall mechanics: When a good diaphragm does not suffice to take a good breath in. Respiratory medicine case reports 15: 20-3	Case report n=2	The inspiratory action of the diaphragm does not only depend on diaphragm contractile properties, but also of a diaphragm “contractile environment” that includes diaphragm geometry, abdominal compliance, and rib cage compliance. It is also a reminder that breathing is intimately dependent on, and interferes with, spinal cord and costovertebral joints mechanics. That a “good diaphragm” is not sufficient to produce a “good inspiration” must be kept in mind when managing people with diaphragm pacing.	Small sample
Le Pimpec-Barthes F, Gonzalez-Bermejo J, Hubsch JP et al. (2011) Intrathoracic phrenic pacing: a 10-year experience in France. The Journal of thoracic and cardiovascular surgery 142(2): 378-83	Case series n=20 follow up: 36 months	VATS implantation of 4-pole electrodes around the intrathoracic PN is a safe procedure. Ventilatory weaning correlates with the degree of diaphragmatic amyotrophy. Phrenic pacing, performed as soon as neurologic and orthopaedic stabilisation is achieved, is the most important prognostic factor for successful weaning.	Small sample with mixed indications, short follow up

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Miller JI, Farmer JA, Stuart W et al. (1990) Phrenic nerve pacing of the quadriplegic patient. The Journal of thoracic and cardiovascular surgery 99(1): 35-40	Case series n=23 (SCI, n=21) follow up: 6 years	PNP in people with quadriplegia is a useful modality when appropriate patient selection, meticulous surgical technique and appropriate PN testing and training are completed. Excellent results can be anticipated. Long-term success depends on adequate follow up, support of the medical and surgical team, and the dedicated care and support of the person's family.	Small sample, more recent studies included
Nakajima K, Sharkey PC (1990) Electrophrenic respiration in patients with craniocervical trauma. Stereotact Funct Neurosurg 54-55:233-6	Case series n=15	Of the 15 people, 11 achieved full-time respiration with electrophrenic respiration and another 2 achieved half-time respiration. Despite the loss of people due to unrelated problems, 7 now use electrophrenic respiration continuously, 1 for 18 years.	Small sample with mixed indications; more recent studies included
Sharma V, Jafri H, Roy N et al. (2021) Thirty-six-month follow-up of diaphragm pacing with phrenic nerve stimulation for ventilator dependence in traumatic tetraplegia: the way forward for spinal cord injury rehabilitation in a developing country. Asian spine journal 15(6): 874-80	Case report n=1 follow up: 36 months	At 36 months after implantation, the person is ventilator-free without any procedure-related complications or respiratory infections. Diaphragm pacing with PNP may be a way forward for ventilator-dependent people with tetraplegia in developing countries to pursue effective rehabilitation and improved quality of life.	Small sample
Sieg EP, Payne R A, Hazard S et al. (2016) Evaluating	Systematic review	The quality of the published literature for PN stimulation is poor. The literature	No meta-analysis, mixed indications,

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the evidence: is phrenic nerve stimulation a safe and effective tool for decreasing ventilator dependence in patients with high cervical spinal cord injuries and central hypoventilation? Child's nervous system: ChNS: official journal of the International Society for Pediatric Neurosurgery 32(6): 1033-8	18 articles (class IV evidence)	review suggests that PNP is a safe and effective option for decreasing ventilator dependence in high SCI and central hypoventilation; however, there are critical questions that provide crucial directions for future studies.	number of people with SCI unclear, and outcomes for SCI not reported separately. More recent studies (in the systematic review) included in the key evidence
Sharkey PC, Halter JA and Nakajima K (1989) Electrophrenic respiration in patients with high quadriplegia. Neurosurgery 24(4):529–35	Case series n=15	Thirteen people (86%) achieved full-time respiration and 2 more achieved half-time respiration. Despite the loss of 8 people to unrelated problems, 7 now use electrophrenic respiration continuously, 1 having done so for 16 years. The cervical approach is preferred. Complications consisted primarily of equipment failures.	Small sample; more recent studies included
Son BC, Kim DR, Kim II-S et al. (2013) Phrenic nerve stimulation for diaphragm pacing in a quadriplegic patient. Journal of Korean Neurosurgical Society 54(4): 359-62	Case report n=1 follow up: 12 months	After diaphragmatic pacing, the person who was completely dependent on the mechanical ventilator could ambulate up to 3 hours every day without aid of MV during the 12 months of follow up. Diaphragm pacing through unilateral PNP with spinal cord stimulator was feasible in an apnoeic person with complete quadriplegia who was completely dependent on MV. Diaphragm pacing with the spinal cord	Small sample

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		stimulator is feasible and effective for the treatment of CHS.	
Tibballs J (1991) Diaphragmatic pacing: an alternative to long-term mechanical ventilation. Anaesthesia and intensive care 19(4): 597-601	Case report n=1	During pacing, the fenestrated tracheostomy tube is capped, thus enabling inspiration of normally humidified air and normal phonation on exhalation. During sleep MV is administered via the tracheostomy.	Small sample
Vanderlinden RG, Epstein SW, Hyland RH et al. (1988) Management of chronic ventilatory insufficiency with electrical diaphragm pacing. The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques 15(1): 63-7	Case series n=24	Diaphragm pacing is the treatment of choice for people who are ventilator= dependent and have tetraplegia from upper cervical trauma or in some cases of neurogenic apnoea; it may be life saving for people who suffer central alveolar hypoventilation.	Small sample with mixed indications. More recent studies included
Watt J, Wiredu E, Silva P et al. (2011) Survival after short- or long-term ventilation after acute spinal cord injury: a single-centre 25-year retrospective study. Spinal Cord 49: 404-10	Non-randomised comparative study (retrospective) n=189 (19 people had diaphragm pacing)	The survival time for people with high tetraplegia on long-term ventilation compares with other datasets and older people have a proportionately greater loss in life expectancy. Self-ventilating people with tetraplegia remain at considerable risk from respiratory death and consideration needs to be given to more effective preventative measures.	Small number of people who had diaphragm pacing. Lack of information on the type of intervention (PNP)
Weese-Mayer DE, Morrow AS, Brouillette RT et al. (1989) Diaphragm pacing in infants and children. A life-	Case series n=33	The diaphragm pacing system is effective but not without risk of biomedical component failure. The system might be substantially improved by 1)	Mixed indications and outcomes for SCI not reported separately.

IP overview: phrenic nerve pacing for ventilator-dependent high cervical spinal cord injury

table analysis of implanted components. The American review of respiratory disease 139(4): 974-9		a modified receiver design with a hermetic seal to prevent fluid penetration, 2) stronger, better insulated electrode wires, and 3) modifications of surgical technique and electrode type to prevent PN damage.	More recent studies included
Weese-Mayer DE, Silvestri JM, Kenny AS et al. (1996) Diaphragm pacing with a quadripolar phrenic nerve electrode: an international study. Pacing and clinical electrophysiology: PACE 19(9): 1311-9	Analysis of questionnaire and registry data n=64	Although pacer complications were not increased among children as compared to adults, the incidence of complications was highest among the active children with CCHS. Longitudinal study of these people will provide invaluable information for modification and improvement of the quadripolar system.	Mixed indications and outcomes for SCI not reported separately. More recent studies included