

Interventional procedure overview of phrenic nerve pacing for congenital central hypoventilation syndrome

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Table 1 Abbreviations

Abbreviation	Definition
ABD	Avery biomedical devices
BiPAP	Bilevel positive airway pressure
CCAHS	Congenital central alveolar hypoventilation syndrome
CCHS	Congenital central hypoventilation syndrome
DP	Diaphragm pacing
IQR	Interquartile range
MV	Mechanical ventilation
OSA	Obstructive sleep apnoea
PN	Phrenic nerve
PNP	Phrenic nerve pacing
PPV	Positive pressure ventilation
SD	Standard deviation
VATS	Video assisted thoracoscopic surgery

Indications and current treatment

CCHS is a rare genetic condition, with around 1,000 cases identified worldwide. CCHS affects how the autonomic nervous system manages or controls breathing. Normally, when breathing is shallow while asleep, the levels of carbon dioxide in the blood increase, which stimulates breathing. In CCHS, this stimulus does not happen, and breathing can stop. Common symptoms include difficulty breathing (especially during sleep), hypercapnia and hypoxemia. So, lifelong ventilatory support is needed during sleep or all the time.

There is no cure for CCHS, but the symptoms can be managed. As CCHS can affect several systems in the body, it needs to be managed by several medical

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teams (multidisciplinary approach). For respiratory insufficiency, the common treatment includes PPV by tracheostomy or mask to assist with breathing.

Unmet need

Most people with CCHS need lifelong ventilatory support using a mechanical ventilator. Most of them only need support during sleep and some also need daytime assistance with breathing. While some people will remain ventilated by MV, many people may benefit from PNP, especially older children and adults who have hidden daytime hypoventilation. PNP allows breathing without the need for a tracheostomy or mask ventilation, maintaining mobility and potentially improving quality of life.

What the procedure involves

PNP involves the direct stimulation of the PN sending 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 thoracoscopic 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 works. This procedure is usually

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done bilaterally and can also be done unilaterally. A cervical approach can also be used and is done under general or local anaesthesia, but this is less common.

Outcome measures

The main outcomes included daily pacing duration, decannulation of tracheostomy, return to productivity, implant longevity, revision, PN damage and other complications.

Evidence summary

Population and studies description

This interventional procedure overview is based on 1,562 people who had the procedure from 4 case series (Ali 2008; Diep 2015; Nicholson 2015; Tsolakis 2022) 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](#).

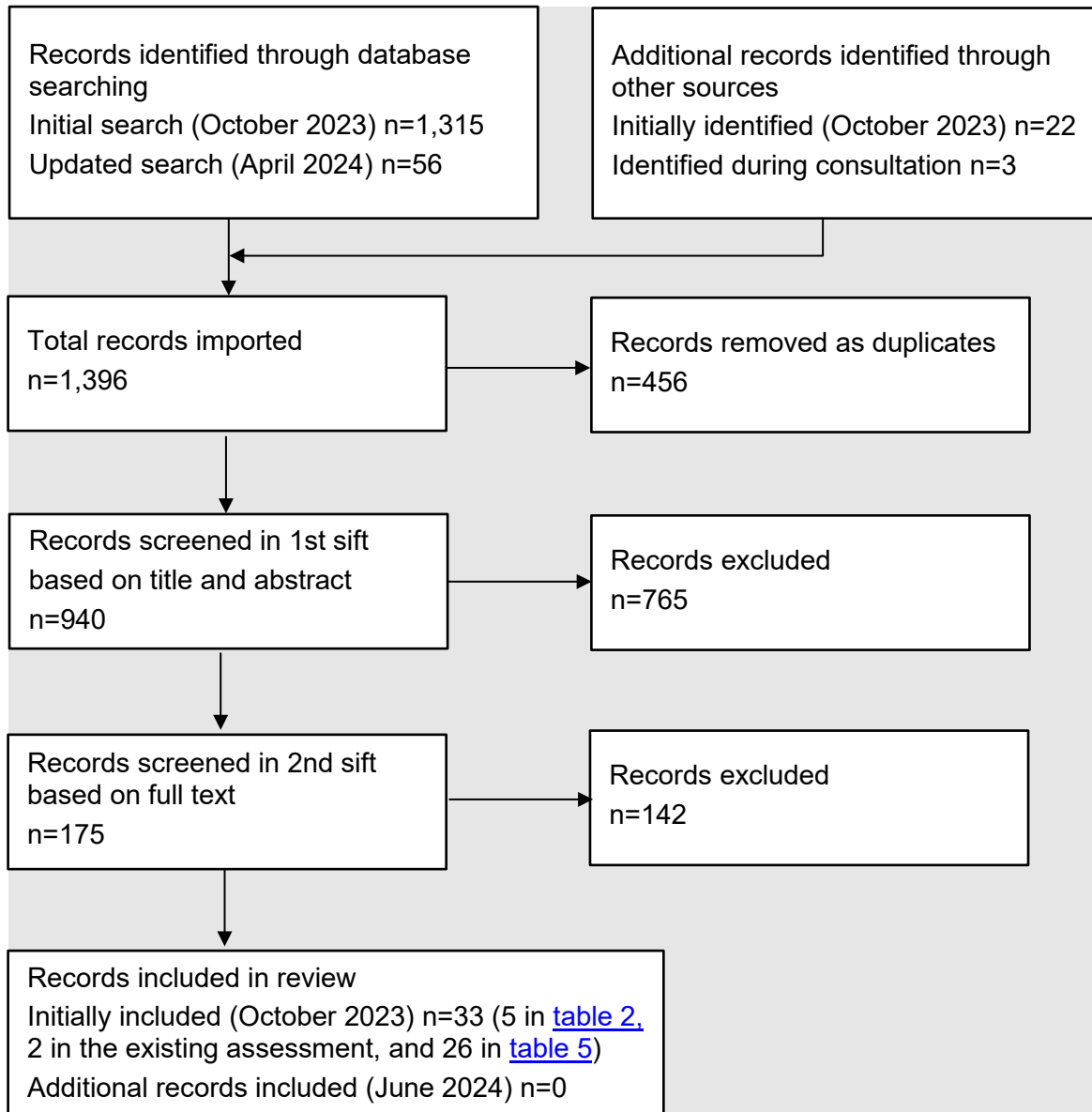
Of the 4 case series included in the key evidence, 2 case series (Diep 2015; Nicholson 2015) were done in the US, 1 case series (Ali 2008) in Canada, and 1 case series (Tsolakis 2022) in Sweden. All 4 case series included people with CCHS, with a total of 63 people (31 male and 32 female). The reported age was mean 4 years (Ali 2008), median 5.7 years (Nicholson 2015) and mean 9 years (Diep 2015; Tsolakis 2022). The follow-up or observational duration was from mean 3 to 10 years across 3 studies and potentially around 30 years for 1 study. In 3 case series (Diep 2015; Nicholson 2015; Tsolakis 2022) with 59 people, PHOX2B mutations were confirmed in 50 people.

The analysis of the ABD database (Headley 2023) included people with different indications (including CCHS) and potentially from multiple countries, but the

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exact number of people with CCHS was not reported. But, it reviewed the data collected for 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 the 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	Diep (2015) US (single centre)	18 (10:8)	Mean 9.6 years (SD 6.4)	Case series (retrospective)	People with CCHS who were ventilator-dependent only during sleep and received PNP	Intrathoracic placement of PN pacers (Avery devices), with majority having pacers implanted thoracoscopically	Mean 10 years after implantation
2	Nicholson (2015) US (single centre)	18 (10:8)	17 patients: median 5.7 years (IQR 4.5 to 12.1) 1 patient with a revision: 34.9 years	Case series (retrospective)	People with CCHS who received PNP	Thoracoscopic placement of PN pacers, usually using 3 trocars per hemithorax. Primary operation (bilateral): n=17 Revision of an original procedure before the study period (unilateral): n=1	Mean 33.7 months after implantation
3	Ali (2008) Canada (single centre)	6 (2:4)	Mean 4 years	Case series (retrospective)	People with CCAHS in the diaphragmatic pacing programme	Thoracic placement of PN pacers (Avery device), mainly bilateral axillary thoracotomy: <ul style="list-style-type: none"> • Thoracotomy (open technique): n=4 	Mean 10 years of pacing

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Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
						<ul style="list-style-type: none"> • Thoracoscopic (minimally invasive technique): n=1 • Both: n=1 	
4	Tsolakis (2022) Sweden (single centre)	23 (10:13) CCHS, n=21 Others, n=2	Mean 9.1 years	Case series (retrospective)	People with CCHS who were ventilator-dependent mainly during sleep and received PNP	(Cervical) placement of PN pacers	About 30 years
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)	About 38 years
<p>Studies 1 to 4 were retrospective, non-comparative studies with small samples (particularly in Ali 2008 [n=6]), and the key biases included selection bias, missing data and outcome reporting bias (particularly in Ali 2008 and Tsolakis 2022).</p> <p>About Headley (2023), the key limitations included retrospective in nature, a lack of baseline characteristics, bias in classification of intervention (as the database was only for 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 CCHS) were reported.</p>							

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Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Diep B (2015)	<p>Total sample: n=18</p> <p>Mode of ventilation before PNP:</p> <ul style="list-style-type: none"> • Home portable PPV by tracheostomy: n=14 • MV/PPV by endotracheal tube: n=1 • Non-invasive PPV by nasal mask: n=2 • Non-invasive PPV by nasal mask with tracheostomy capped: n=1 <p>Full nighttime PNP after initiation: 89% (16/18) at a mean of 6.6 (SD 7.5) months (range 2.5 to 32.5) from surgery. One patient was on full nighttime PNP after 3 years, as they and their family opted to only use DP when a nurse was present.</p> <p>Of the 16 patients with full nighttime PNP, 1 patient was paced for 7 years and then returned to during non-invasive PPV because of significant weight gain.</p> <p>Tracheostomy decannulation: 73% (11/15) at a mean of 12.2 months (SD 11.0).</p> <p>Obstacles to decannulation: obesity (n=1), severe upper airway obstruction with inspiration (n=1), social reasons (n=1), seizures and developmental delay (n=1)</p> <p>Ventilation with PNP without tracheostomy: 72% (13/18)</p>	<p>No major intraoperative complications.</p> <p>Shoulder pain: All patients had intrathoracic PN electrodes, and while shoulder pain could occur when the tidal volume was too high, the pain was relieved when the tidal volume was reduced.</p> <p>Snoring and/or obstructive apnoea in some patients (exact number not reported): symptoms were improved by pacer setting changes (decreased tidal volume during polysomnography), adenotonsillectomy, or use of nasal steroids.</p>
Nicholson (2015)	Total sample: n=18	Persistent atelectasis: n=3, with 1 progressing to pneumonia.

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First author, date	Efficacy outcomes	Safety outcomes
	<p>At baseline, tracheostomy in 15 patients and BiPAP during sleep in 3 patients</p> <p>Length of ICU stay: mean 4.3 days (SD 0.5)</p> <p>Length of hospital stay: mean 5.7 days (SD 0.3)</p> <p>Daily pacing goal:</p> <ul style="list-style-type: none"> • 11 patients achieved the goal at a mean follow up of 5.3 months (SD 2.2) after PNP. 7 patients had their tracheostomies successfully decannulated at a mean follow up of 12.5 months (SD 5.2). • 1 patient with revision procedure (because of mechanical failure – secondary to faulty wiring insulation on the pacing device) achieved the goal and subsequently tracheostomy successfully decannulated during a 20-month follow up. • Unable to achieve the daily pacing goal: n=2 • Lost to follow up: n=4 	<p>Two-minute generalised tonic clonic seizure on day 2: n=1, likely secondary to hypercarbia, with pCO₂ transiently measured in the 90s mmHg. Following aggressive suctioning, pCO₂ was maintained in the 40s mmHg with no further seizure activity.</p> <p>One patient who had the procedure before the study period returned to the hospital twice during the study period for replacement of the receiver portion of the pacing apparatus. This repair needed only a small abdominal incision, and the portion of the device contained within the thorax was not disturbed. No long-term complications.</p>
Ali (2008)	<p>Total sample: n=6</p> <p>At baseline, 3 patients presented with asphyxia, 2 with apnoea and 1 was unable to wean from ventilation.</p> <p>PNP during the day and MV at night: n=6</p> <p>Daily pacing hours:</p> <ul style="list-style-type: none"> • 8 to 10 hours: n=3 • 10 to 12 hours: n=3 <p>Authors preferred to limit the period of pacing to 12 hours per day to minimise the risk of PN damage.</p>	<p>Equipment replacement: n=5</p> <ul style="list-style-type: none"> • Receiver replacement: n=4 (2 on 1 side and 2 on both sides), with the mean time to failure of a receiver being 96.9 months • Wire/electrode changes: n=4 (2 on the right side and 2 on the left side), with a mean time to change a wire being 8.8 years <p>One patient had both infectious complications and equipment failure. The patient had subcutaneous pocket infection at 1 month postoperatively and subsequently developed an</p>

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First author, date	Efficacy outcomes	Safety outcomes
	<p>All patients were usually admitted annually for minor adjustments of the pacer. They all led an active life, attending school full time and/or working. Some were even involved in intramural team sports.</p>	<p>empyema on the same side 3 years later. Their electrode was eventually replaced in the neck. They developed unwanted secondary brachial plexus twinges, for which revision was again done.</p> <p>PN damage:</p> <ul style="list-style-type: none"> • Axonal damage to the left phrenic nerve: n=1 who had been paced for 13 years • No phrenic nerve damage: n=5 at a mean pacing of 10 years (2.5 to 21 years)
Tsolakis (2022)	<p>Total sample: n=23 (18 patients used non-invasive ventilation and 5 had a tracheostomy before implantation)</p> <p>Decannulation of tracheostomy: 100% (5/5) within 6 months after procedure.</p> <p>Successful transition to PNP (complete change to sleep-assisted, non-MV): 87% (20/23)</p> <p>13% (3/23) of patients continued with non-invasive ventilation.</p> <p>Years spent pacing: Some patients used PNP for 30 years without needing replacement electrodes or receivers (exact data not reported)</p> <p>Overseas patients (n=12) could not be followed up, but their respective hospitals reported that they were doing well.</p>	Not reported
Headley (2023)	<p>Total sample: n=1,522 (3,478 devices implanted)</p> <p>Years spent pacing:</p>	<p>Revision surgeries for the I-110 receiver (current version): n=172 of 854 patients implanted with the I-110 receiver.</p>

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First author, date	Efficacy outcomes	Safety outcomes
	<p>Pacing for over 40 years: n=3 active patients; n=2 deceased patients</p> <p>Pacing for over 30 years: n=33 active patients; n=8 deceased patients</p> <p>Longevity of implants: 6.5 years (median, 5; SD 6.2) no significant difference in the amount of time implants last between cervical (mean 6.4 years; SD 6.8) and thoracic (mean 6.4 years; SD 5.7) approaches (p=0.9382).</p> <p>Survey results (n=111):</p> <ul style="list-style-type: none"> • Tracheostomy removal: 76% of respondents had a tracheostomy before implantation, and of these patients, about 33% chose to have them removed following implantation. • Patient-reported daily amount of time spent pacing: <ul style="list-style-type: none"> ○ 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 ○ 16 to 20 hours daily: 13% of respondents ○ 24/7: 16% of respondents 	<p>Electrode revision: 169 out of 962 patients (47 with unknown location) needed revision, with a total of 209 revisions (change location, n=47)</p> <ul style="list-style-type: none"> • patients with cervical approach: 66 out of 380 patients (17%) needed revision, with a total of 82 revisions (change cervical to thoracic location, n=37 [45%]; no change to location, n=25) • patients with thoracic approach: 95 out of 518 patients (18%) needed revision, with a total of 113 revisions (change thoracic to cervical location, n=10 [10%]; no change to location, n=77) • patients with 1 side cervical and 1 side thoracic implantation: 7 out of 9 patients needed revision, with a total of 14 revisions <p>Reasons for revision for cervically implanted PN pacers:</p> <ul style="list-style-type: none"> • no report/no problem found: 18% • surgical placement of implants: 14% • intermittent (loss of stimulation): 14% • insultation damage: 12% • damage to wire: 9% • calcification of anode: 8% • accidental damage (sports): 6% • accidental damage (medical treatment): 5% • infection after surgery: 5%

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First author, date	Efficacy outcomes	Safety outcomes
		<ul style="list-style-type: none"> • twiddler: 4% • patient growth: 5% <p>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.</p>

Procedure technique

Of the 4 case series, 3 case series described the procedure technique but varied in detail, while 1 case series (Tsolakis 2022) only mentioned the cervical approach to implantation. When reported, the common device used was the Avery diaphragm pacing system.

To assess the PN integrity, the nerve was stimulated transcutaneously and the response of the diaphragm was monitored using fluoroscopy (Ali 2008). The PN pacers were then implanted either by an open thoracotomy or a thoracoscopic technique. Two case series (Nicholson 2015; Diep 2015) published in 2015 mainly used a thoracoscopic approach to implant the PN pacers, while another (Ali 2008) reported the common approach being thoracic placement of the PN pacers. One probable explanation for the different techniques used was that the thoracoscopic approach (VATS) became a breakthrough method during the late 1990s and early 2000s. The procedure was usually done bilaterally and the mean operative time was 3.3 hours (Nicholson 2015).

After the procedure, pacing was attempted at week 1 (Ali 2008). The median time to initiation of pacing was 2.6 months (Nicholson 2015) with a mean of 2.8 months (Diep 2015). Diaphragmatic conditioning took a mean of 2.7 months (Nicholson 2015) to 6.6 months (Diep 2015).

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 that revealed 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 the 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

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opposed to cervical. Also, thoracic placement of the electrodes was more common in paediatric cases.

Efficacy

Daily pacing duration and decannulation of tracheostomy

Daily pacing duration was reported in all 5 studies and the proportion of people who were paced during sleep, or for 7 hours and above, ranged from 65% to 100%. When reported, successful tracheostomy decannulation was present in 64% of people or above.

In the Diep (2015) study of 18 people with CCHS who were ventilator-dependent only during sleep, 15 people had PPV by tracheostomy, 1 person had PPV by endotracheal tube and 2 people had PPV by nasal mask at baseline. At a mean of 6.6 months after pacing initiation (about 10 months after implantation), 89% (16/18) of people achieved full nighttime PNP. Of the 15 people with tracheostomy before PNP, 73% (11/15) of people were decannulated successfully at a mean follow up of 12.2 months after implantation. At about 10 years after implantation, 72% (13/18) of people were successfully ventilated by PNP without tracheostomy (1 person paced for 7 years without tracheostomy and then returned to using non-invasive PPV because of obesity), 22% (4/18) of people used PNP with tracheostomy and 6% (1/18) of people had only non-invasive PPV. The authors found that obstacles to decannulation included obesity, severe upper airway obstruction, seizures and developmental delay, as well as social reasons.

In the Nicholson (2015) study of 18 people with CCHS, 15 people had tracheostomies and 3 people used BiPAP during sleep at baseline. At a mean of 5.3 months after implantation, 65% (11/17) of people who had primary placement of PN pacer achieved the daily pacing goal (PNP only used during sleep without

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assistance when awake, or 12 to 14 hours of pacing daily maximum). Of the 11 people with primary implantation, 64% (7/11) of people had successful tracheostomy decannulation at a mean of 12.5 months after implantation. For the 1 person who had a revision of an original operation, during a follow up of 20 months, this person achieved the daily pacing goal and subsequently had their tracheostomy decannulated.

In the Ali (2008) study of 6 people with CCAHS, 3 people had asphyxia, 2 had apnoea and 1 person was unable to wean from ventilation at baseline. After several months of diaphragmatic conditioning, all people were paced during the day (3 people with daily pacing of 8 to 10 hours and 3 people with daily pacing of 10 to 12 hours) but were mechanically ventilated at night because the authors preferred to limit the period of pacing to 12 hours to minimise the risk of PN damage.

In the Tsolakis (2022) study of 23 people with CCHS, 18 people were on non-invasive ventilation and 5 had a tracheostomy before implantation. After implantation, 87% (20/23) of people successfully transitioned to PNP (complete change to sleep-assisted, non-MV) and 13% (3/23) of people continued with non-invasive ventilation. All 5 people were decannulated within 6 months after implantation. Some people used PNP for 30 years without needing replacement electrodes or receivers (exact data not reported).

In the analysis of the ABD database, Headley (2023) reported that, of the 111 people who responded to the survey, 57% of respondents reported they were 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 spent 40 years pacing (3 active people and 2 deceased people in the database), and 41 people spent over 30 years pacing (33 active people and 8 deceased people). The survey results also showed that 76% of respondents had a tracheostomy before implantation,

and of these people, around 33% chose to have them removed following implantation.

Return to productivity

Ali (2008) reported that all 6 people led an active life, attended school or worked full time during a 10-year period. Some were even involved in intramural team sports.

Implant longevity

Implant longevity was shown by years in between revision surgeries and presented in 2 studies. Headley (2023) who reviewed the ABD database of 1,522 patients found that the mean longevity was 6.5 years (SD 6.2) for both cervical and thoracic approaches. When comparing the 2 approaches, there was no statistically significant difference in device longevity (cervically implanted device: mean 6.4 years, SD 6.8; thoracically implanted device: mean 6.4 years, SD 5.7; $p=0.9382$). In Ali (2008), the mean time to failure of a receiver was 8.1 years and the mean time to change of a wire was 8.8 years.

Safety

Revision

Revision or device replacement was reported in 3 studies. Headley (2023) reported that, of the 854 people implanted with the current version of the receiver (I-110), 20% (172/854) needed revision surgeries. For the electrodes, 17% (66/380) of cervical cases needed at least 1 revision of the electrode compared with 18% (95/518) of thoracic cases. Data showed that in people initially implanted cervically, 45% of electrode revisions involved moving the electrode placement to the chest compared with 10% of people whose implants were

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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%
- 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%
- twiddler (people who play or nervously fidget with their subcutaneously placed receivers): 4%
- patient growth: 5%

Ali (2008) reported that, of the 6 people with CCAHS, equipment replacement happened in 5 people, including receiver replacement (n=4, 2 people on 1 side and 2 people on both sides) and wire or electrode changes (n=4; 2 people on the right side and 2 people on the left side). More than 1 replacement of the receiver or wire on the same side was found in 2 people (Ali 2008).

In the Nicholson (2015) study of 18 people with CCHS, 1 person who had the procedure before the study period returned to the hospital twice during the study period for a replacement of the receiver portion of the pacing apparatus. This repair needed only a small abdominal incision, and the portion of the device contained within the thorax was not disturbed.

PN damage

PN damage was presented in 2 studies. Ali (2008) reported that, of the 6 people with CCAHS, axonal damage to the left PN was seen in 1 person who had been

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pacing for 13 years. There were no PN damages found in other people during a mean pacing of 10 years. Headley (2023) found that, of the 3,478 implants, PN injury caused by surgical manipulation of the nerve was found in 6 cases over 38 years (less than 0.2%). In 5 of the 6 cases the nerve function recovered.

Respiratory complications

Atelectasis was described in the Nicholson (2015) study. Of the 18 people with CCHS, 3 people had persistent atelectasis after PN pacemaker implantation, with 1 progressing to pneumonia.

Infectious complications

In the Ali (2008) study of 6 people with CCAHS, 1 person had both infectious complications and equipment failure. This person also had a subcutaneous pocket infection 1 month after surgery and subsequently developed an empyema on the same side 3 years later. Their electrode was eventually replaced in the neck. They developed unwanted secondary brachial plexus twinges, for which revision was again done (Ali 2008).

Tonic clonic seizure

Seizure was presented in the Nicholson (2015) study. Of the 18 people with CCHS, 1 person with no medical history of seizure disorder experienced a 2-minute generalised tonic clonic seizure 2 days after implantation, likely secondary to hypercarbia, with pCO₂ transiently measured in the 90s mmHg. After aggressive suctioning, pCO₂ was maintained in the 40s mmHg with no further seizure activity.

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

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: those expected for an implantable neurostimulation device, repeated surgical intervention, risk of general anaesthetic, and post operative risks.

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

Validity and generalisability

All 5 studies were retrospective. Four case series included small samples (6 to 21 people with CCHS), with 2 case series (Nicholson 2015; Diep 2015) reporting outcomes at mean 3 and 10 years after implantation, and 1 study by Ali (2008) reporting results at mean 10 years after pacing. Loss to follow up was 6% (Diep 2015) to 22% (Nicholson 2015). Tsolakis (2022) reported 30-year pacing in some people. Also, 12 international referrals could not be followed up, so the dropout rate was 52%.

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

When reported, only 1 paper's authors had conflicts of interest (Headley 2023) and 1 reported no conflict of interest (Tsolakis 2022).

Although the daily pacing duration was reported in all studies, the outcomes reported varied. The review of the ABD database provided the revision data, reported the implant longevity and detailed the reasons for revision. But, as the procedure technology and the devices used are evolving, this would potentially

affect the safety and efficacy profiles of the procedure, in particular the device longevity. As noted by Ali (2008) and Headley (2023), as the device gets more and more refined, it lasts longer.

Overall, the evidence shows that the proportion of people who were paced during sleep, or for 7 hours and above, ranged from 65% to 100%. The key factors that prevented successful PNP without tracheostomy (decannulation of tracheostomy) were obesity and (severe) upper airway obstruction (Diep 2015). Two people who had cardiac pacemakers placed for syncope or bradycardia on Holter monitoring were included in the Nicholson (2015) study, but no particular concerns were highlighted. To avoid interference with a PN pacer, the use of bipolar cardiac pacing electrode was preferred (Weese-Mayer 2010; Trang 2020).

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, showing that the rate of revision surgeries for the I-110 receiver (current version) was 20%. Other complications, such as PN damage, were rare.

Nevertheless, the evidence is limited and there is a lack of evidence on survival, reduction in respiratory complications, and quality of life. But, it is noted that CCHS is a rare genetic condition which would limit evidence generation, and to date, no ongoing trials have been identified.

Existing assessments of this procedure

In 2009 the American Thoracic Society (ATS) published an official clinical policy statement on CCHS (Weese-Mayer 2010). ATS stated that diaphragm pacing can be one of the options to provide chronic artificial ventilation for children with CCHS at home as they do not usually have lung disease. ATS also mentioned that bilateral implantation of PN electrodes and diaphragm pacer receivers is

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recommended to achieve optimal ventilation in children. For people with CCHS who may need cardiac pacemakers in addition to diaphragm pacers, both can be used together in the same person without interference as long as the cardiac pacemaker is bipolar, thereby minimising the potential for electromagnetic interference with the bilateral monopolar PN electrodes.

In 2020, the European CCHS Consortium Project guidelines for diagnosis and management of congenital central hypoventilation syndrome were published (Trang 2020). The guidelines covered infants, children and adults with CCHS. The guideline development group recommended PNP to be one of the options for ventilatory support, stating:

- Mask ventilation requires a cooperative person with normal airway and either adequate spontaneous ventilation or PNP during wakefulness.
- PNP offers freedom from the ventilator during daytime in people ventilated 24 hours per day, so increasing mobility and allowing for sporting and professional activities.
- To avoid interference with a PN pacer, the use of bipolar cardiac pacing electrode is preferred.

Related NICE guidance

Interventional procedures

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

Professional societies

- British Paediatric Respiratory Society
- British Paediatric Neurosurgical group
- British Paediatric Neurology Association
- Paediatric Critical Care Society
- Association of British Neurologists
- Society of British Neurological Surgeons
- British Thoracic Society
- British Sleep Society

Evidence from patients and patient organisations

NICE received 1 submission from a patient organisation about PNP for CCHS.

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

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2. Nicholson KJ, Nosanov LB, Bowen KA et al. (2015) Thoracoscopic placement of phrenic nerve pacers for diaphragm pacing in congenital central hypoventilation syndrome. *Journal of pediatric surgery* 50(1): 78-81.

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3. Ali A and Flageole H (2008) Diaphragmatic pacing for the treatment of congenital central alveolar hypoventilation syndrome. *Journal of pediatric surgery* 43(5): 792-6
4. Tsolakis N, Sindelar R, Markstrom A et al. (2022) Strategy of changing from tracheostomy and non-invasive mechanical ventilation to diaphragm pacing in children with congenital central hypoventilation syndrome. *Acta paediatrica* (Oslo, Norway: 1992) 111(6): 1245-7
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6. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I et al. (2010) An official ATS clinical policy statement: congenital central hypoventilation syndrome. *Am J Respir Crit Care Med*, 181: 626–44.
7. Trang H, Samuels M, Ceccherini I et al. (2020) Guidelines for diagnosis and management of congenital central hypoventilation syndrome. *Orphanet Journal of Rare Diseases*, 15:252

Methods

NICE identified studies and reviews relevant to phrenic nerve pacing for congenital central hypoventilation syndrome 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. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.

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- Patients with congenital central hypoventilation syndrome.
- Intervention or test: phrenic nerve pacing.
- 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

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)

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- 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.
- 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

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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
Domanski MC and Preciado DA (2012) Vocal cord collapse during phrenic nerve-paced respiration in congenital central hypoventilation syndrome. F1000Research 1: 42	Case report n=1	No abnormal vocal cord stimulation was witnessed during engaging of either phrenic nerve stimulator. However, the lack of normal inspiratory vocal cord abduction during phrenic nerve-paced respiration resulted in vocal cord collapse and partial obstruction due to passive adduction of the vocal cords through the Bernoulli effect. Bilateral phrenic nerve stimulation resulted in more vocal cord collapse than unilateral stimulation.	Small sample
Flageole H, Adolph VR, Davis GM et al. (1995) Diaphragmatic pacing in children with congenital central alveolar hypoventilation syndrome. Surgery 118(1): 25-8	Case series n=3 follow up: 6 months to 10 years	Paediatric surgeons should be aware of CCAHS because it may be treated with surgically implanted electrodes that allow for pacing of the diaphragm. The technique has an acceptable complication rate, and it can greatly decrease the impact of the disease on the lifestyle and activity of the patient. CCAHS also may be associated with Hirschsprung's disease.	Small sample; more recent studies included.

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<p>Fitzgerald D, Davis GM, Gottesman R et al. (1996) Diaphragmatic pacemaker failure in congenital central hypoventilation syndrome: a tale of two twiddlers. Pediatric pulmonology 22(5): 319-21</p>	<p>Case reports n=2</p>	<p>Authors recommend that the chest radiographs that are undertaken to investigate diaphragmatic pacemaker dysfunction include the internal implant. As these cases illustrate, the chest radiograph will not necessarily demonstrate a reason for dysfunction of the pacemaker, although pacing wire coiling on a radiograph should suggest wire discontinuity from twiddling as a likely cause of pacemaker failure.</p>	<p>Small sample; more recent studies included.</p>
<p>Fodstad H (1989) Pacing of the diaphragm to control breathing in patients with paralysis of central nervous system origin. Stereotactic and functional neurosurgery 53(4): 209-22</p>	<p>Case series n=35 follow up: mean 46 months</p>	<p>At a mean follow-up time of 46 months, 15 patients are entirely independent of respirator and 8 quadriplegics ventilate with pacers at different daytime intervals and use mechanical ventilators during the night. Five patients have stopped pacing and 7 additional cases have died of causes unrelated to electrophrenic stimulation.</p>	<p>Mixed indications and outcomes for CCHS not reported separately. More recent studies included.</p>
<p>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</p>	<p>Case series n=22</p>	<p>Evidence shows that complete stable ventilation can be achieved using diaphragmatic pacing and that it improves the prognosis and life quality of patients with severe chronic respiratory failure.</p>	<p>Mixed indications and outcomes for CCHS not reported separately. More recent studies included.</p>
<p>Glenn WWL, Brouillete RT, Dentz B et al. (1988) Fundamental</p>	<p>Case series (retrospective)</p>	<p>Key recommendations: 1. A program to assure long-term follow-up of patients by physicians and</p>	<p>Mixed indications and key outcomes for CCHS not reported separately. More</p>

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<p>considerations in pacing of the diaphragm for chronic ventilatory insufficiency: a multi-centre study. PACE, 11: 2121-7</p>	<p>n=475 (CCHS, n=35)</p>	<p>paramedical personnel knowledgeable in pacing; 2. Facilities for regular monitoring of pacemaker performance and patient 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 patients who have had a diaphragm pacemaker implanted, with detailed study of the phrenic nerve and diaphragm muscle to determine the effects of electrical stimulation on these vital structures: Pathological studies will provide definitive factual information needed to determine the future role of diaphragm pacing in the treatment of chronic ventilatory insufficiency and which will be applicable to other neuromuscular stimulation.</p>	<p>recent studies included.</p>
<p>Hirschfeld S, Huhtala H, Thietje R et al. (2022) Phrenic nerve stimulation experiences. A single centre, controlled, prospective study. Journal of clinical neuroscience: official journal of the Neurosurgical Society of</p>	<p>Non-randomised comparative study n=92 (CHS, n=2)</p>	<p>With PNS, authors found a tendency towards better survival compared to MV. The frequency of decubital ulcers and urological complications appear significantly more with MV than with PNS, proving enhanced mobility and facilitation of nursing with PNS. Patients prefer PNS and refuse randomisation, which may be taken as their opinion of the improved quality of</p>	<p>Small sample</p>

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Australasia 101: 26-31		life with PNS. The frequency of respiratory infections differed highly significantly in favour of PNS. Large savings are subsequently obvious.	
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.	More recent studies included.
Ilbawi MN, Idriss FS, Hunt CE et al. (1985) Diaphragmatic pacing in infants: techniques and results. The Annals of thoracic surgery 40(4): 323-9	Case series n=8	PNP can be done safely in infants. It provides an effective alternative method for ventilatory support without the drawbacks of positive pressure ventilation.	Small sample; more recent studies included.
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 (CCHS, n=1) follow up: 1 to 21 years	The data suggests that phrenic nerve stimulation can be used instead of mechanical ventilators for long-term ongoing respiratory support.	Small sample
Kolb C, Eicken A, Zrenner B et al. (2006) Cardiac pacing in a patient with diaphragm pacing for congenital central hypoventilation syndrome	Case report n=1 follow up: 3 months	Patients with idiopathic congenital central hypoventilation syndrome (Ondine's curse) may develop an indication for cardiac pacing due to bradyarrhythmias. Cardiac pacing in the presence of a unipolar diaphragm	Small sample

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(Ondine's curse). Journal of cardiovascular electrophysiology 17(7): 789-91		pacing system is feasible and safe if thorough testing for possible interdevice interactions is done. However, the experience gained from this patient is not transferable to the implantation of other cardiac pacing systems, such as implantable cardioverter defibrillators, because the sensing behaviour is significantly different in these devices.	
Kwon A, Lodge M, McComb JG et al. (2022) An unusual cause of diaphragm pacer failure in congenital central hypoventilation syndrome. Journal of clinical sleep medicine: JCSM : official publication of the American Academy of Sleep Medicine 18(3): 949-52	Case report n=1	This case suggests that calcium can encase DP receivers and that calcium deposition can accumulate to a significant amount over time. This case also underscores how increasing distance from skin surface, such as that occurring with weight gain, can interfere with DP function. Calcification of internal DP components is an uncommon cause of DP failure but suggests that calcium deposition and accumulation should be considered when evaluating patients for DP malfunction and/or failure, especially in those who have used DP long-term. The case emphasises the importance of routine follow-up and periodic evaluation of DP function to confirm optimal performance.	Small sample
Le Pimpec-Barthes F, Gonzalez-Bermejo J, Hubsch	Case series	Video-assisted thoracic surgery implantation of 4-pole electrodes around	Small sample

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<p>JP et al. (2011) Intrathoracic phrenic pacing: a 10-year experience in France. The Journal of thoracic and cardiovascular surgery 142(2): 378-83</p>	<p>n=20 (CCHS, n=1) follow up: 36 months</p>	<p>the intrathoracic phrenic nerve is a safe procedure. Ventilatory weaning correlates with the degree of diaphragmatic amyotrophy. Phrenic pacing, done as soon as neurologic and orthopaedic stabilisation is achieved, is the most important prognostic factor for successful weaning.</p>	
<p>Pino-Diaz L, Leu RM and Kasi AS (2020) Polysomnographic artifacts in a child with congenital central hypoventilation syndrome. J Clin Sleep Med. 16(12):2123–5</p>	<p>Case report n=1</p>	<p>This paper reports a 14-year-old boy with CCHS who uses DP with an uncapped tracheostomy during sleep. Polysomnography to titrate DP settings identified artifacts occurring in regular intervals coinciding with the onset of inspiration during all sleep stages in several channels including legs, snore, and electrocardiogram. Clinicians interpreting polysomnograms done during DP should become familiar with the multichannel artifacts due to DP impulses. The patient was hyperventilated on home DP settings that led to adjustment of DP settings during the polysomnogram to achieve optimal oxygenation and ventilation. This case also highlights the utility of polysomnography to ensure optimal gas exchange during sleep in</p>	<p>Small sample</p>

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		children with CCHS using DP.	
Shah AS, Leu RM, Keens TG et al. (2021) Annual respiratory evaluations in congenital central hypoventilation syndrome and changes in ventilatory management. Pediatric allergy, immunology, and pulmonology, 34 (3)	Case series (retrospective) n=10 (tracheostomy, n=7; diaphragm pacing, n=3)	This paper reports a high prevalence of changes in assisted ventilation management following an annual in-hospital respiratory evaluation. The results show the importance of regular annual in-hospital respiratory evaluations in patients with CCHS to assess their ventilatory requirements and optimise assisted ventilation.	Small sample, aiming to determine if annual in-hospital respiratory evaluations (Polysomnography with capnography) in patients with CCHS led to changes in ventilatory management.
Shaul DB, McComb, JG and Keens TG (1998) Thoracoscopic placement of phrenic nerve electrodes for diaphragm pacing. Pediatric Endosurgery and Innovative Techniques 2(3): 101-5	Case report n=1 follow up: 6 weeks	Phrenic nerve electrodes for diaphragm pacing were successfully implanted in a 14-year-old girl by thoracoscopy. This was associated with successful diaphragm pacing and an improvement in the patient's condition.	Small sample
Sieg E P, Payne R A, Hazard S et al. (2016) Evaluating 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	Systematic review 18 articles (class 4 evidence)	The quality of the published literature for phrenic nerve stimulation is poor. The literature review suggests that PNS 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.	No meta-analysis, mixed indications (mainly SCIs), number of patients with CCHS unclear, and outcomes for CCHS not reported separately. More recent studies included in the key evidence.

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the International Society for Pediatric Neurosurgery 32(6): 1033-8			
Shaul DB, Danielson PD, McComb JG et al. (2002) Thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing in children. Journal of pediatric surgery 37(7): 974-8	Case series n=9 follow up: 30 months	Phrenic nerve electrodes can be implanted thoracoscopically and allow the successful use of diaphragmatic pacing therapy. Avoidance of thoracotomy with its associated perioperative morbidity and scarring may encourage wider utilisation of diaphragmatic pacing in children.	Small sample; more recent studies included.
Takeda S, Fujii Y, Kawahara H et al. (1996) Central alveolar hypoventilation syndrome (Ondine's curse) with gastroesophageal reflux. Chest 110(3): 850-2	Case report n=1	Trials for removal of the tracheostomy tube were unsuccessful due to upper airway obstruction during pacing. Except for a minor complication of wire breakage, the diaphragm pacing was uneventful and the patient was discharged from the hospital and continued electrophrenic respiration at home.	Small sample
Tibballs, James and Henning, Robert D (2003) Noninvasive ventilatory strategies in the management of a newborn infant and three children with congenital central hypoventilation syndrome. Pediatric pulmonology 36(6): 544-8	Case series n=4 (PNP, n=1)	Authors suggest that management of a newborn diagnosed with CCHS could initially be with nasal mask BiPAP upon cessation of mechanical ventilation by endotracheal tube in the first few weeks of life. Tracheostomy can be avoided. However, preparations should be made to trial negative pressure chamber or cuirass ventilation as soon as practicable, to avoid	Small sample; more recent studies included.

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		the problems of midface hypoplasia and pseudoprognathism associated with prolonged nasal mask BiPAP. If upper airway obstruction occurs during negative pressure ventilation, limited mask CPAP may be beneficial. If hypoventilation is present during wakefulness, phrenic nerve pacing is the only practical alternative from the time the patient becomes ambulant, but airway obstruction during sleep with this technique may limit its usefulness.	
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 patients who are ventilator-dependent and tetraplegic from upper cervical trauma or in some cases of neurogenic apnoea; it may be life saving for patients with central alveolar hypoventilation.	Small sample with mixed indications and outcomes for CCHS not reported separately. More recent studies included.
Valika T, Chin AC, Thompson DM et al. (2019) Airway obstruction during sleep due to diaphragm pacing precludes decannulation in young children with CCHS.	Case series n=3	Further research is needed to understand paediatric and adult airway physiology with unopposed pacer-induced diaphragm contractions as published literature has shown success of decannulation with phrenic nerve-diaphragm	Small sample

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Respiration; international review of thoracic diseases 98(3): 263-267		pacing in some older children and adults.	
Wang A, Kun S, Diep B et al. (2018) Obstructive sleep apnea in patients with congenital central hypoventilation syndrome ventilated by diaphragm pacing without tracheostomy. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine 14(2): 261-4	Case series n=15	OSA occurs in patients with CCHS ventilated by DP. However, decreasing DP amplitude settings can lessen upper airway obstruction without compromising gas exchange.	Polysomnography – sleep study
Weese-Mayer DE, Morrow AS, Brouillette RT et al. (1989) Diaphragm pacing in infants and children. A life- table analysis of implanted components. The American review of respiratory disease 139(4): 974-9	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) 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 phrenic nerve damage.	Mixed indications and outcomes for CCHS not reported separately. More recent studies included.
Weese-Mayer DE, Silvestri JM, Kenny AS et al. (1996) Diaphragm pacing with a quadripolar phrenic nerve	Analysis of questionnaire and registry data	Although pacer complications were not increased among paediatric as compared to adult patients, the incidence of complications	Mixed indications and outcomes for CCHS not reported separately. More

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<p>electrode: an international study. Pacing and clinical electrophysiology: PACE 19(9): 1311-9</p>	<p>n=64</p>	<p>was highest among the active paediatric patients with CCHS. Longitudinal study of these patients will provide invaluable information for modification and improvement of the quadripolar system.</p>	<p>recent studies included.</p>
<p>Yasuma F, Nomura H, Sotobata I et al. (1987) Congenital central alveolar hypoventilation (Ondine's curse): a case report and review of the literature. European journal of pediatrics 146(1): 81-3</p>	<p>Case report n=1 Follow up: 2 years</p>	<p>At a 2-year follow up, the patient respiratory status was satisfactory with overnight diaphragm pacing at home.</p>	<p>Small sample</p>