Diaphragm Pacing without Tracheostomy in Congenital Central Hypoventilation Syndrome Patients

Bonnie Diep a  Annie Wang a  Sheila Kun b  J. Gordon McComb c
Donald B. Shaul e  Cathy E. Shin d  Thomas G. Keens b  Iris A. Perez b

a Keck School of Medicine of the University of Southern California, and Divisions of b Pediatric Pulmonology and Sleep Medicine, c Pediatric Neurosurgery and c Pediatric Surgery, Children’s Hospital Los Angeles, Keck School of Medicine of the University of Southern California, and e Southern California Permanente Medical Group, Kaiser Permanente Los Angeles Medical Center, Los Angeles, Calif., USA

Abstract
Background: Congenital central hypoventilation syndrome (CCHS) is a rare disorder affecting central control of breathing. Thus, patients require lifelong assisted ventilation. Diaphragm pacing (DP) may permit decannulation in those who are ventilator dependent only during sleep. Objective: The purpose of this study is to determine if patients with CCHS can be successfully ventilated by DP without tracheostomy. Methods: We reviewed the records of 18 CCHS patients (mean age 19.5 ± 10.1 years; 44% female) who were ventilated by DP only during sleep. Results: Prior to diaphragm pacer implantation surgery, 14 CCHS patients had been using home portable positive pressure ventilation (PPV) via tracheostomy, 1 had been on PPV via endotracheal tube, and 3 had been using noninvasive PPV (NPPV). Of the patients with tracheostomy prior to DP (n = 15), 11 (73%) were decannulated and ventilated successfully by DP without tracheostomy. Of all the patients reviewed (n = 18), 13 (72%) were successfully ventilated by DP without tracheostomy. Obesity prevented successful DP without tracheostomy in 1 patient, and upper airway obstruction prevented success in another patient. Snoring and/or obstructive apneas were present in some patients, but they were improved by diaphragm pacer changes, adenotonsillectomy, and/or use of nasal steroids. Conclusions: DP without tracheostomy can be successfully achieved in patients with CCHS. Snoring and obstructive apneas, when present, can be managed by diaphragm pacer changes and medical therapies. Obesity can pose a challenge to successful DP.

Introduction

Congenital central hypoventilation syndrome (CCHS) is a genetic disorder with failure of central control of breathing and of the autonomic nervous system due to a mutation in the PHOX2B gene [1–5]. Affected patients usually present in infancy with absent or negligible ventilatory sensitivity to hypercapnia and hypoxemia that is worse during sleep than wakefulness. They require lifelong assisted ventilation during sleep or 24 h a day [1, 2, 5]. Most patients receive assisted ventilation using positive pressure ventilation (PPV) via tracheostomy [1, 2,
5–9]. Some families choose to use ventilatory support without a tracheostomy, such as noninvasive PPV (NPPV) [9–14], diaphragm pacing (DP) [8, 9, 15–19], or negative pressure ventilators [9, 20]. DP via phrenic nerve stimulation has been used for over four decades in infants and children [15–18]. It allows full-time ventilator-dependent CCHS patients to be free of PPV during the day, allowing mobility and independent living. In those who are ventilator dependent only during sleep, DP may permit decannulation of the tracheostomy.

There are currently no published data on the successful outcome of DP without tracheostomy in CCHS patients who are ventilator dependent only during sleep. Thus, we performed this retrospective study of CCHS patients who underwent DP implantation surgery. We hypothesized that many CCHS patients who are ventilator dependent only during sleep can be ventilated successfully without tracheostomy by DP.

**Methods**

The Children’s Hospital Los Angeles (CHLA) follows 51 CCHS patients, 23 of whom have received diaphragm pacers. We reviewed the records of the 19 CCHS patients who were ventilator dependent only during sleep and received DP at the CHLA from January 1980 to January 2013. The diagnosis of CCHS was confirmed by genetic testing in 16 patients. One patient was excluded as he was lost to follow-up. Therefore, data on the remaining 18 patients are reported.

CCHS patients who were ventilated by DP during sleep were reviewed for the following information: (1) age, (2) type of assisted ventilation prior to DP (NPPV or PPV via tracheostomy), (3) time from diaphragm pacer surgical implantation to initiation of pacing, (4) time from DP initiation to all-night DP, (5) time from DP surgery to decannulation, (6) obstacles to decannulation, and (7) interventions to improve ventilation via DP. Successful transition to DP was defined as complete transition to assisted ventilation during sleep via DP without tracheostomy.

This study was approved by the Institutional Review Board of the CHLA.

**Results**

**Patient Characteristics**

Eighteen patients were included in the study, 44% female, with a mean age at diaphragm pacer implantation of 9.6 ± 6.4 years (range 1.5–23.5). PHOX2B mutations were confirmed in 16 patients. Ten patients had a 20/25 polyalanine repeat expansion mutation (PARM), 1 patient had a 20/26 PARM, 3 patients had a 20/27 PARM, 1 patient had a 20/33 PARM, and 1 patient had a novel p.82 mutation. Two patients were not tested. The body mass index (BMI) and BMI z-scores (for patients 5–19 years old during their clinic visit) were calculated for each patient. Two patients were overweight and 2 patients were obese based on cutoffs by the World Health Organization. All patients in our study required assisted ventilation only during sleep. The patients’ characteristics are listed in table 1.

**Mode of Ventilation Prior to DP**

Prior to diaphragm pacer implantation surgery, 14 patients had received assisted ventilation using home portable PPV via tracheostomy. One patient never had a tracheostomy, since she had been on mechanical ventilation via endotracheal tube until she was 17 months old, which was when the diaphragm pacers were initially placed. Two patients were already decannulated, and they had used NPPV via nasal mask prior to surgery. One patient had her tracheostomy already capped while she was awake and asleep and had been receiving NPPV via nasal mask prior to her evaluation for DP.

**Outcome following Diaphragm Pacer Surgery**

Seventeen CCHS patients had diaphragm pacer implantation surgery at the CHLA. There were no major intraoperative complications. One patient had already been receiving DP prior to transferring her care to the CHLA. All patients received the Mark IV (Avery Biomedical Devices, Inc.) diaphragm pacer system with intrathoracic placement of electrodes. The majority had their diaphragm pacers implanted thoracoscopically as described by Shaul et al. [20].

The mean age at DP implantation was 9.6 ± 6.4 years (range 1.5–23.5), with the youngest patient undergoing implantation surgery at 17 months of age. DP was initiated at a mean of 2.8 ± 2.2 months (range 0.5–10.2) following surgery. Sixteen of the 18 patients (89%) achieved full nighttime DP after initiation at a mean of 6.6 ± 7.5 months (range 2.5–32.5) from surgery. One patient was on full nighttime DP after 3 years, as he and his family opted to use DP only when a nurse was present.

Eleven (73%) of the 15 patients with tracheostomy prior to DP were decannulated successfully. Thirteen of the total of 18 patients (72%) were successfully ventilated by DP without tracheostomy. One patient who had been receiving nasal NPPV but had a tracheostomy was decannulated 2 weeks after the pacer implantation surgery. The mean age at decannulation was 12.6 ± 7.1 years (range 5.2–28.4). Decannulation was performed at a mean of 12.2 ± 11.0 months (range 0.6–40.6) from diaphragm pacer implantation surgery. One patient’s values were not included in the calculation of the mean. He had develop-
mental delay, and the patient and his family did not want him decannulated until 25 years after the diaphragm implantation. Of the patients who had a tracheostomy, all had met the criteria for pacing without tracheostomy prior to decannulation as set in our DP program at the CHLA and as noted in Table 2 [16].

Shoulder pain with DP using intradiaphragmatic phrenic nerve stimulation was reported by Morélot-Panzini et al. [21]. All of our patients had intrathoracic phrenic nerve electrodes, and while shoulder pain can occur when the tidal volume is too high, the pain is relieved when the tidal volume is reduced.

Obstructive apnea can occur when DP is used without tracheostomy. In order to successfully decannulate these patients, some had to have changes in DP pacemaker settings (decreased tidal volume). Two patients had an adenotonsillectomy prior to decannulation. Three patients were on nasal steroids. Snoring was present in virtually all patients. Adequate ventilation was generally improved by diaphragm pacemaker settings changes that were performed during polysomnography.

### Polysomnography

Polysomnography data were not available for all patients before and after decannulation. Only 1 patient had polysomnography data before and after decannulation. Six patients underwent polysomnography with their tracheostomy capped prior to decannulation. These patients did not show obstructive sleep apneas. Five patients underwent polysomnography after decannulation.

Of the patients who underwent polysomnography after decannulation, 1 had obstructive sleep apnea. Initially, this patient’s apnea-hypopnea index was 3.4, indicating mild obstructive sleep apnea syndrome, with the lowest SpO₂ 79% and the highest P_EtCO₂ 58 mm Hg. After slight adjustment of the tidal volume settings, her apnea-hypopnea index dropped to 1.7, with the lowest SpO₂ 92% and the highest P_EtCO₂ 33 mm Hg.

### Obstacles to Decannulation

Two patients did not achieve full nighttime pacing after diaphragm pacemaker surgery. One patient decided not to use pacing, since he did not like how it felt, and returned...
Diaphragm Pacing without Tracheostomy

During spontaneous breathing in normal individuals, there is synchronous contraction of the upper airway skeletal muscles with diaphragm contraction to maintain airway patency. During DP, this synchronous contraction is bypassed, predisposing the upper airways to collapse due to the negative intrathoracic pressure created by the diaphragm contraction and absent upper airway skeletal muscle contraction. Younger children and infants are more susceptible to this due to their smaller airway dimensions and the mid position of their vocal cords at rest [15, 18]. The lack of synchrony between upper airway skeletal muscles and the diaphragm has been suggested as the pathogenesis for upper airway obstruction in previous case reports. We did not conduct upper airway electromyography in our study. However, the authors cannot overemphasize the importance of assessing the upper airway anatomy by otolaryngology and performance of polysomnography with a capped tracheostomy tube prior to any consideration of decannulation. During endoscopy, the upper airway is evaluated to rule out anatomical and functional abnormalities, such as granulomas. During performance of a polysomnography with the tracheostomy capped, the diaphragm pacer settings can be adjusted to achieve optimal gas exchange, and alleviate obstructive apneas, if present, as discussed below. Even if it may not be possible to eliminate all obstructive hypopneas, DP can still be used if an adequate gas exchange is achieved.

Snoring and obstructive apneas were present in our study; however, in general, making changes in the diaphragm pacer settings alleviated these issues. We have successfully managed obstructive apneas by performing polysomnography to assess and change the pacer settings. We

In our study, we considered this patient to have successfully achieved DP without tracheostomy, since she had been pacing for 7 years before her weight gain. Two other patients were considered overweight, but they did not have problems with DP. All other patients had a BMI or BMI z-score that was normal.

Four patients with tracheostomy have not been decannulated. One patient preferred to keep his tracheostomy for social reasons. One patient had severe upper airway obstruction with inspiration documented during polysomnography with the tracheostomy tube briefly removed, despite changing the DP settings, which prevented decannulation. He had normal airway examinations performed by his otolaryngologist prior to the sleep study. Decannulation was electively delayed in 1 patient due to seizures and developmental delay. As discussed previously, obesity was an obstacle in 1 patient, who was unable to progress to full nighttime pacing with tracheostomy.

**Discussion**

Our study shows that CCHS patients who are ventilator dependent only during sleep can be ventilated successfully by DP without tracheostomy. Most patients without comorbidities who are ventilator dependent via tracheostomy can be successfully decannulated.

Upper airway obstruction can be a complication of DP without tracheostomy [16, 22, 23]. During spontaneous breathing in normal individuals, there is synchronous contraction of the upper airway skeletal muscles with diaphragm contraction to maintain airway patency. During DP, this synchronous contraction is bypassed, predisposing the upper airways to collapse due to the negative intrathoracic pressure created by the diaphragm contraction and absent upper airway skeletal muscle contraction. Younger children and infants are more susceptible to this due to their smaller airway dimensions and the mid position of their vocal cords at rest [15, 18]. The lack of synchrony between upper airway skeletal muscles and the diaphragm has been suggested as the pathogenesis for upper airway obstruction in previous case reports. We did not conduct upper airway electromyography in our study. However, the authors cannot overemphasize the importance of assessing the upper airway anatomy by otolaryngology and performance of polysomnography with a capped tracheostomy tube prior to any consideration of decannulation. During endoscopy, the upper airway is evaluated to rule out anatomical and functional abnormalities, such as granulomas. During performance of a polysomnography with the tracheostomy capped, the diaphragm pacer settings can be adjusted to achieve optimal gas exchange, and alleviate obstructive apneas, if present, as discussed below. Even if it may not be possible to eliminate all obstructive hypopneas, DP can still be used if an adequate gas exchange is achieved.

Snoring and obstructive apneas were present in our study; however, in general, making changes in the diaphragm pacer settings alleviated these issues. We have successfully managed obstructive apneas by performing polysomnography to assess and change the pacer settings. We

---

**Table 2. Criteria for pacing without tracheostomy and protocol for decannulation**

<table>
<thead>
<tr>
<th>Criteria for pacing without tracheostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHS requiring ventilatory support only during sleep</td>
</tr>
<tr>
<td>Not requiring daytime naps</td>
</tr>
<tr>
<td>Stable medical course requiring infrequent hospitalizations</td>
</tr>
<tr>
<td>Not requiring full-time ventilatory support during acute respiratory illnesses</td>
</tr>
<tr>
<td>Acceptance that DP is not as secure a method of ventilation and intubation may be required for serious illness</td>
</tr>
</tbody>
</table>

**Protocol for decannulation**

- Establish adequate ventilation with DP using an open tracheostomy for ≥3 months
- Downsize tracheostomy
- Overnight polysomnography with DP and tracheostomy capped:
  - if SpO2 <95% and P_{ETCO2} <40 mm Hg, consider supplemental O2 via nasal cannula
  - if OSA is present, consider decreasing tidal volume in diaphragm pacer settings, tonsillectomy/adenoidectomy, and treating nasal allergies; repeat sleep study
  - if SpO2 >95% and P_{ETCO2} <40 mm Hg and no OSA is present, conduct airway evaluation by ENT; if normal, proceed to decannulation
- Overnight hospital observation after decannulation

OSA = Obstructive sleep apnea.
decreased the tidal volume to decrease the force of inspira-
tion with each diaphragm contraction. Some other patients
responded to treating nasal allergies and/or performing ad-
tonotsillectomy. Despite these changes, the obstructive
apneas were too severe in 1 patient, so that we were unable
to decannulate him. Prolonging the inspiratory time would
theoretically also decrease the force of inspiration and al-
leviate obstructive apneas. However, in our series, we were
successful by decreasing the tidal volume instead.

Obesity is an obstacle to successful DP, as seen in 2 of
our patients. We attribute this to an increased distance
between the antenna and the receiver resulting from large
amounts of adipose tissue in the current pathway from
the receiver to the antenna. Changing body positions,
which can compress or increase the distance between
the antenna and the receiver, may result in decreased or in-
creased diaphragm contractions. When a patient is lying
on her antenna, the fat is compressed, decreasing the dis-
tance between the receiver and the antenna, resulting in
stronger diaphragm contraction. However, while lying
supine, there is a greater distance between the receiver
and the antenna, resulting in decreased diaphragm con-
traction. With obesity, there is an inability to find a con-
sistent diaphragm pacer setting to achieve adequate ven-
tilation. This suggests that obesity is a contraindication to
DP, and weight control and counseling should be part of
the initial assessment and follow-up of obese patients
about to receive DP.

In conclusion, many CCHS patients who require ven-
tilatory support only during sleep can be successfully ven-
tilated by DP without tracheostomy. Although upper air-
way obstruction can occur due to the absence of synchro-
nous upper airway skeletal muscle contraction with
diaphragm contraction, changes in DP settings and other
medical management can usually relieve this, facilitating
tracheostomy decannulation.

References


2. Weese-Mayer DE, Berry-Kravis EM, Ceccheri-
ni, Ni, Keens TG, Loghmane DA, Trang H: An
offical ATS clinical policy statement: congeni-
tal central hypoventilation syndrome: genetic
basis, diagnosis, and management. Am J Respir

3. Amiel J, Laudier B, Attie-Bitach T, Trang H, de
Pontual L, Gener B, Trochet D, Etchevers H,
Ray P, Simonneau M, Vekemens M, Munnich
A, Gaultier C, Lyonnet S: Polyalanine expan-
sion and frameshift mutations of the paired-
like homeobox gene PHOX2B in congenital cen-
tral hypoventilation syndrome. Nat Genet

4. Matera I, Bachetti T, Puppo F, Di Duca M, Mor-
andi F, Carisarigh GM, Cilio MR, Hennekam R,
Hostra R, Schober JG, Ravazzolo R, Ottonello
G, Ceccherini I: PHOX2B mutations and poly-
alanine expansions correlate with the severity
of the respiratory phenotype and associated
symptoms in both congenital and late onset
central hypoventilation syndrome. J Med Gen-

5. Chen ML, Keens TG: Congenital central hypo-
ventilation syndrome: not just another rare

6. Keens T, Davidson Ward S: Syndromes affect-
ing respiratory control during sleep; in Lough-
lin G, Marcus C, Carroll J (eds): Sleep and
Breathing in Children: A Developmental Ap-
proach. New York, Marcel Dekker, 2000, pp
525–555.

7. Wittmans M, Chen M, Davidson Ward S, Keens
T: Congenital syndromes affecting respiratory
control during sleep; in Lee-Chiong T (ed):
Sleep: A Comprehensive Handbook. Hoboken,

8. Perez I, Keens T, Ward S: Noninvasive positive
pressure ventilation in the treatment of hyper-
aventilation in children. Sleep Med Clin 2010;
3:471–484.

A, Gozal D: Epidemiologic survey of 196 pa-
tients with congenital central hypoventilation

10. Kerbl R, Litscher H, Grubbauer HM, Reiterer P,
Zobel G, Trollo M, Uuslander B, Eber E, Kurz
R: Congenital central hypoventilation syn-
drome (Ondine’s curse syndrome) in two sib-
lings: delayed diagnosis and successful noninva-

11. Tibbals J, Henning RD: Noninvasive ventila-
tory strategies in the management of a newborn
infant and three children with congenital cen-
tral hypoventilation syndrome. Pediatr Pulmo-

12. Villa MP, Dotta A, Castello D, Piro S, Pagani J,
Palamides S, Ronchetti R: Bi-level positive air-
way pressure (BiPAP) ventilation in an infant
with central hypertensive ventilation. Pediatr

13. Glenn WW, Holcomb WG, Gee JB, Rath R:
Central hyperventilation; long-term ventilatory
assistance by radiofrequency electrophrenic

14. Windisch W, Hennings E, Store JH, Matthys
H, Sorichter S: Delayed survival of a patient
with congenital central hypoventilation syn-
drome despite the lack of continuous ventila-

15. Chen ML, Tablizo MA, Kun S, Keens TG: Dia-
aphragm pacers as a treatment for congenital
central hypoventilation syndrome. Expert Rev

16. Glenn WW, Phelps ML: Diaphragm pacing by
electrical stimulation of the phrenic nerve.

17. Hunt CE, Brouillette RT, Weese-Mayer DE,
McCorvie A, Ilbawi MN: Diaphragm pacing in
infants and children. Pacing Clin Electrophysi-

18. Weese-Mayer DE, Hunt CE, Brouillette RT, Sil-
vestri JM: Diaphragm pacing in infants and chil-

19. Hartmann H, Jawad MH, Noyes J, Samuels
MP, Southall DP: Negative extrathoracic pres-
sure ventilation in central hyperventilation syn-

20. Shaul DB, Danielson PD, McComb JG, Keens
TG: Thoracoscopic placement of phrenic nerve
electrodes for diaphragmatic pacing in chil-
sion 974–978.

21. Morélot-Panzini C, Gonzalez-Bermejo J,
Straus C, Similowski T: Reversal of pulmonary
hypertension after diaphragm pacing in an
adult patient with congenital central hypo-
ventilation syndrome. Int J Artif Organs 2013;36:
434–438.

22. Reverdin AK, Mosquera R, Colasurdo GN, Jon
CK, Clements RM: Airway obstruction in con-
genital central hypoventilation syndrome. BMJ

23. Hyland RH, Hutcheon MA, Perl A, Bowes G,
Anthonisen NR, Zamal N, Phillipsen EA: Up-
per airway occlusion induced by diaphragm
pacing for primary alveolar hyperventilation:
implications for the pathogenesis of obstructive

 DOI: 10.1159/000381401

Respiration 2015;89:534–538

Diep/Wang/Kun/McComb/Shaul/Shin/Keens/Perez