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Thoracoscopic placement of phrenic nerve pacers for diaphragm pacing in congenital central hypoventilation syndrome

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ABSTRACT

Purpose: Congenital central hypoventilation syndrome (CCHS), or Ondine's curse, is a rare disorder affecting central respiratory drive. Patients with this disorder fail to ventilate adequately and require lifelong ventilatory support. Diaphragm pacing is a form of ventilatory support which can improve mobility and/or remove the tracheostomy from CCHS patients. Little is known about complications and long-term outcomes of this procedure.
Methods: A single-center retrospective review was performed of CCHS patients undergoing placement of phrenic nerve electrodes for diaphragm pacing between 2000 and 2012. Data abstracted from the medical record included operation duration, ventilation method, number of trocars required, and postoperative and pacing outcomes.
Results: Charts of eighteen patients were reviewed. Mean surgical time was 3.3 ± 0.7 hours. In all cases except one, three trocars were utilized for each hemithorax, with no conversions to open procedures. Five patients (27.8%) experienced postoperative complications. The mean ICU stay was 4.3 ± 0.5 days, and the mean hospital stay is 5.7 ± 0.3 days. Eleven patients (61.1%) achieved their daily goal pacing times within the follow-up period.
Conclusions: Thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing is a safe and effective treatment modality for CCHS. Observed complications were temporary, and the majority of patients were able to achieve pacing goals.

Congenital central hypoventilation syndrome (CCHS), or Ondine's curse, is a rare disorder affecting central respiratory drive. It is most commonly caused by a polyalanine repeat expansion mutation on exon 3 of the homeobox gene, PHOX2B, on the p arm of chromosome 4 [1], which is involved in normal neuron genesis and migration during fetal development. Those with longer expansions of the gene tend to manifest a more severe phenotype [2]. Ten percent of patients have nonpolyalanine repeat mutations of the PHOX2B gene [3], and these patients often demonstrate the most severe phenotypes [4]. Most patients with CCHS are identified perinatally, presenting with alveolar hypoventilation and other autonomic dysfunction. Patients with this disorder fail to ventilate adequately, particularly while sleeping, and therefore require lifelong ventilatory support [5]. In addition to hypoventilation, patients with CCHS also have a higher incidence of other neurologic disorders, including Hirschprung disease, autonomic nervous system dysfunction, developmental delay, bradycardia, and neural crest tumors [3].

Patients with this disorder fail to ventilate adequately, particularly while sleeping, and require lifelong ventilatory support [5]. Thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing, as a method of ventilatory support, can enhance mobility in patients requiring full-time support, and remove the tracheostomy in patients requiring support only during sleep. Phrenic nerve pacing can be offered to patients who do not have intrinsic lung disease, are not obese, and have an intact phrenic nerve-diaphragm axis [3]. The procedure can be performed in children as young as nine months of age. For patients who are full-time ventilator dependent, pacers may be placed as soon as this determination is made [6]. Patients who are not full-time ventilator dependent and are able undergo decannulation of their tracheostomies following pacer placement may later develop obstructive apnea. Our center therefore prefers to offer the procedure to patients five years of age and older, with the intention of decannulating at age six, as obstructive apnea is less frequently an issue in more developed children.

Approximately 6–8 weeks after the phrenic nerve pacers are placed, patients are admitted to the hospital for initiation of pacing, followed by gradual increases in pacing time in the outpatient setting, until patients achieve their pacing goals [6]. With appropriate monitoring, patients may have their tracheostomies downsized, and eventually decannulated.

As this operation is performed at only a few centers, little is known about complications and long-term outcomes. The objective

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of this study is to define contemporary operative procedure and postoperative outcomes.

1. Methods

After IRB approval, we conducted a retrospective analysis of all children who underwent operative management of CCHS at Children's Hospital Los Angeles between 2000 and 2012. A thorough chart review was performed for all patients meeting inclusion criteria. Data abstracted included patient demographics, details of medical comorbidities and genetic mutation profiles, operative parameters, postoperative outcomes, and outpatient follow-up of clinical progress.

Descriptive statistics were used to define the study population. Normally distributed continuous variables were described by means and standard deviations while nonnormally distributed continuous variables were described by medians and interquartile ranges. Categorical variables were reported using proportions and percentages. All analyses were performed using the Statistical Package for Social Sciences (SPSS Mac©), version 22.0 (IBM Corp., Armonk, NY).

1.1. Operative procedure

The patient is placed in the lateral decubitus position on a bean bag, and prepped and draped in the usual sterile fashion. An incision is made under the tip of the scapula with a 15-blade, and a 5 mm Veress needle is inserted. The hemithorax is insufflated to 10 mm Hg, and a trocar and camera are inserted. Under direct vision, two additional trocars are placed. The phrenic nerve is identified and dissected out proximally (Fig. 1). The electrode is placed behind the phrenic nerve and pexied to the pericardium (Fig. 2). An incision is then made below the costal margin, with a pocket created for the receiver. A clamp is passed through the diaphragm, and the electrode passed from the thorax to the abdominal cavity by grasping a Penrose drain tied around the distal end of the electrode (Fig. 3). This is pulled into place and the Penrose removed. The electrode is then attached to the receiving unit and secured with a 3–0 Ethibond suture. The pacer receiving unit is placed in the subcutaneous pocket. The antenna is placed over the receiver and the unit tested. The diaphragm contracts, indicating that the unit functions satisfactorily. The electrode connection is placed in a Dacron pouch which is closed with a 3–0 Ethibond suture. The area is irrigated with Ringer's lactate containing vancomycin. The fascia is closed with a running 4–0 Vicryl suture, and the skin closed with a subcuticular 4–0 Vicryl suture and Dermabond. The patient is then turned to the other side the operation repeated for the contralateral side.

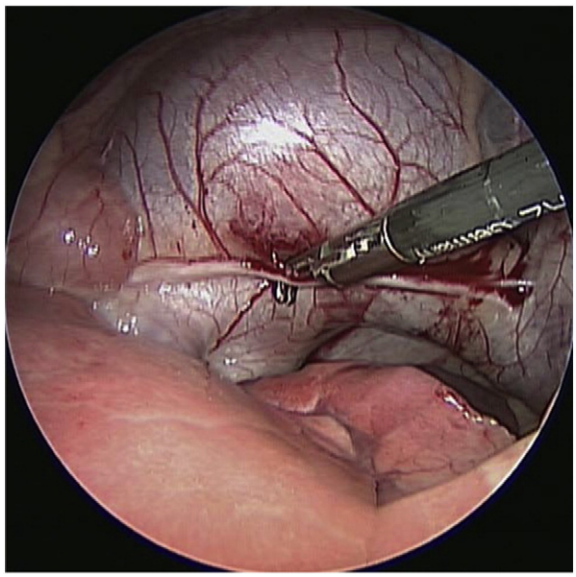

Fig. 1. Electrode placed around the phrenic nerve and sutured to pericardium.

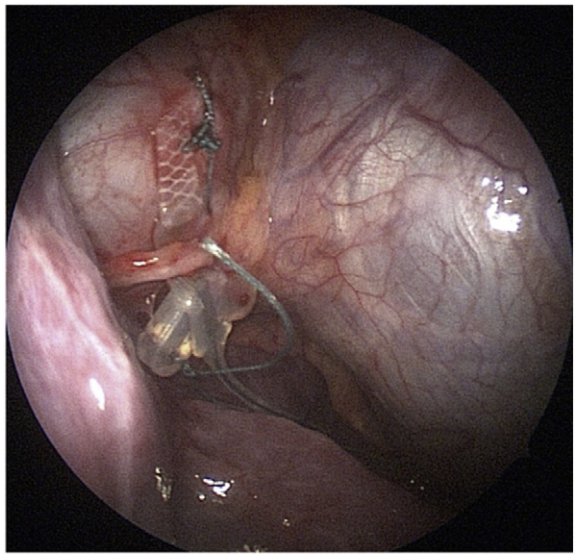

Fig. 2. Electrode connection tunneled through chest wall to subcutaneous pocket.

2. Results

A total of 18 patients undergoing operative management for CCHS during the ten-year study period were identified. Seventeen of these patients underwent primary operations during this time. Median age of this cohort was 5.7 years (IQR 4.5–12.1 years, range 2.7–23.5 years) (Table 1). One patient, at the age of 34.9 years, underwent a revision of an original procedure performed prior to the study period. The patient population was primarily white (38.9%) and male (55.6%). A mutation in the PHOX2B gene was confirmed in all but two patients, one of whom was untested, with the 20/25 mutation being the most common (50.0%). This series includes a mother and her two children, all affected by CCHS [7].

Patients presented with a wide variety of comorbid conditions (Table 2), with a total of 19 conditions seen in 10 patients. Among the more common findings were Hirschsprung's disease (16.7%) and developmental delay (16.7%). Two patients were dependent on enteral feeding via gastrostomy tubes at the time of operation due to esophageal

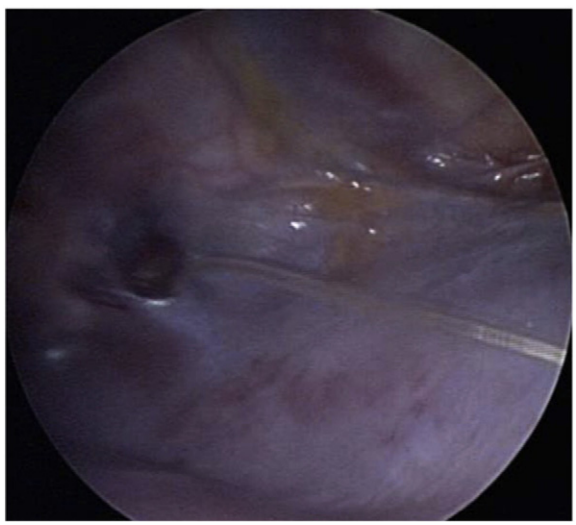

Fig. 3. Results.

Table 1
Demographics.

Age (years, median and IQR)	5.71, 4.50–12.09
Sex (male)	10 (55.6%)
Race	
White	7 (38.9%)
Hispanic	3 (16.7%)
Asian	3 (16.7%)
Other	5 (27.8%)
PHOX2B mutation	
No mutation	2 (11.1%)
20/25	9 (50.0%)
20/26	1 (5.6%)
20/27	5 (27.8%)
p.P82L	1 (5.6%)

Abbreviations: IQR (interquartile range); PHOX2b (paired homeobox-like 2b).

dysmotility, and two had cardiac pacemakers placed for syncope or bradycardia on Holter monitoring.

At the time of operation, all but three patients had previously-placed tracheostomies. These three patients were utilizing BPAP during sleep for ventilatory support. The majority (52.6%) of patients were ventilated during the operation using a contralateral mainstem endotracheal tube, with the remainder utilizing either dual lumen or bronchial blocker tubes.

Most patients had the standard three trocars utilized per hemithorax, while one patient undergoing a first-time operation required placement of an additional left-sided trocar secondary to difficulty with visualization. No procedures performed were converted to open operations. Mean operative time was 3.3 ± 0.7 hours (range 2.2–4.5 hours) for operations including both hemithoraces.

In all patients, one thoracostomy tube was placed in each hemithorax prior to the conclusion of the operation. After confirming the absence of a clinically significant pneumothorax, the majority of patients had both tubes removed. Postoperatively, 7 (36.8%) retained one tube and 2 (10.5%) retained two tubes in order to manage persistent pneumothoraces. One patient had imaging negative for pneumothorax intraoperatively and therefore had both tubes removed, but subsequently was found to have a clinically significant pneumothorax which required placement of a chest tube.

Postoperatively, three patients were found to have persistent atelectasis, with one progressing to pneumonia. One patient with no medical history of seizure disorder experienced a two-minute generalized tonic clonic seizure on postoperative day two, likely secondary to hypercarbia, with pCO_2 transiently measured in the 90's. Following aggressive suctioning, pCO_2 was maintained in the 40's with no further seizure activity. Per protocol, all patients were taken to the intensive care unit postoperatively for ventilator management. Mean length of stay in the ICU was 4.3 ± 0.5 days (range 2.0–8.0 days). Hospital stays averaged 5.7 ± 0.3 days (range 4.0–9.0 days).

Table 2
Comorbidities.

Comorbidity	Frequency
Neurologic/psychiatric	
Seizure disorder	2 (11.1%)
Developmental delay	3 (16.7%)
ADHD	1 (5.6%)
Conductive hearing loss	1 (5.6%)
Gastrointestinal	
Hirschsprung's disease	3 (16.7%)
GERD	2 (11.1%)
G-tube dependence	2 (11.1%)
Other	
Juvenile idiopathic arthritis	1 (5.6%)
Asthma	2 (11.1%)
Cardiac pacing dependent	2 (11.1%)

Abbreviations: ADHD (attention deficit hyperactive disorder); GERD (gastroesophageal reflux disease); G-tube (gastrostomy tube).

Duration of outpatient follow-up averaged 33.7 ± 29.4 months (range 2.0 months to 8.4 years). Median time to initiation of pacing was 2.6 months after the procedure (IQR 2.2–4.5 months). The daily pacing goal established for most patients was to require pacing only in those who are ventilator dependent only during sleep, with no assistance required when awake. One patient, who was full-time ventilator dependent, was determined to require a goal of 12–14 hours of pacing daily maximum. Daily pacing goals were achieved by 11 patients during their observed follow-up period, at an average of 5.3 ± 2.2 months postprocedure (range 2.7–9.7 months). Of these 11 patients, 7 were subsequently able to achieve successful decannulation of their tracheostomies, at an average of 12.5 ± 5.2 months postprocedure (range 7.17–20.90 months). Four patients were lost to follow-up prior to achieving their daily pacing goal. An additional two patients failed to achieve their goals during follow-up, citing shoulder pain and discomfort with pacing as contributing factors.

One patient experienced mechanical failure 8.5 months after the primary operation, secondary to faulty wiring insulation on the pacing device. This patient ultimately required a repeat unilateral operation on the left chest 4.4 years after the initial procedure. This revision procedure was uneventful and the patient was followed for an additional 20 months, during which goal pacing was achieved and no further complications were noted. She subsequently had her tracheostomy successfully decannulated.

One patient who underwent the procedure prior to the study period returned to our institution twice during the study period for replacement of the receiver portion of the pacing apparatus. This repair required only a small abdominal incision, and the portion of the device contained within the thorax was not disturbed.

3. Discussion

Worldwide, only a handful of centers offer thoracoscopic phrenic nerve electrode implantation for the treatment of CCHS. To our knowledge, this study is the largest to date to describe a single-center experience with this procedure. The first thoracoscopic placement of diaphragmatic pacers was described by Shaul et al [8] in 1998. In 2002, the same authors described an initial thirteen-year experience with nine pediatric CCHS patients undergoing thoracoscopic placement of diaphragmatic pacers [9]. More recently, a series of 6 patients demonstrated successful phrenic nerve pacing in all patients, with placement of the pacers performed either via thoracotomy or a cervical approach [10]. Since these first reports, this treatment has been used with increasing frequency. The most recent report cites a rate of approximately 18% [11].

Our data demonstrate that this is a safe procedure, with a relatively short mean operative time of 3.3 hours, consistent with the prior report from our institution [9]. Compared to the previous series, fewer patients experienced short-term complications, and none suffered from any long-term complications. For many patients, this procedure is also effective, with 61% achieving their goal pacing times. In this study, 64% of patients achieving pacing goals were able to have their tracheostomies decannulated during the follow-up period. While device failure with need for reoperation is a real issue for some patients, in our experience, those requiring repair of the pacing system did not experience any more complications or longer operative times upon reoperation.

While our study did not directly address the impact of phrenic nerve pacing on quality of life, it has previously been shown to improve quality of life in patients suffering from high spinal cord injuries. One recent study demonstrated not only improved quality of life, particularly in areas of social functioning, but also increased overall patient survival [12]. In our study group, there were also several anecdotal reports of improved quality of life for patients living with CCHS, who were able to participate in activities that would not be possible for patients still requiring a conventional ventilator.

Thoracoscopic placement of diaphragmatic pacers remains a relatively uncommon procedure, with little literature describing experience

with it. Our experience demonstrates that it is a safe, effective procedure, which may be appropriate for many more patients living with CCHS and requiring ventilatory support.

Appendix A. Discussion

Presented by Kristina Nicholson, Los Angeles, CA.

TODD PONSKY (Akron, OH) Recently there has been a lot of work in actually pacing the diaphragm itself versus the phrenic nerve which eliminates the risk of injury to the nerve. We have had some experience with Ondine's curse doing diaphragm pacing which has worked well. Have you considering pacing the diaphragm itself?

KRISTINA NICHOLSON I do not believe that we have considered pacing the diaphragm directly at our institution. I think at this point we would like to see a little bit more study before looking at that.

UNIDENTIFIED SPEAKER Can you give me some long-term effects? How long does this work? When does it fail? Does the diaphragm just stop responding eventually or does it last for 20 years?

KRISTINA NICHOLSON Device failure is not entirely uncommon. Thank you for your question. Sometimes there are problems with the device with insulation around the wiring. Sometimes the device does require replacement. It doesn't happen in every patient and at this point we don't really know long term what the durability of the device is.

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