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Perioperative outcomes and the effects of anesthesia in congenital central hypoventilation patients

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Abstract

Purpose Patients with congenital central hypoventilation syndrome (CCHS) have autonomic dysfunction and lack ventilatory responses to hypoxemia and hypercarbia and thus are prone to adverse events during general anesthesia. The objective of this study was to describe the perioperative outcomes of patients with CCHS who were undergoing diaphragm pacer (DP) implantation surgeries under general anesthesia.

Methods A retrospective cohort study was conducted on patients with CCHS who underwent DP implantation surgeries at CHLA between January 2000 and May 2016. Charts were reviewed for demographics, *PHOX2B* genotype, ventilatory support, comorbidities, anesthesia administered, and perioperative courses.

Results Of 19 patients with CCHS (58% female) mean age at surgeries was 8.6 ± 5.8 years. Seventeen patients were ventilator-dependent during sleep only; two were ventilator dependent 24 h per day. Mean surgery duration was 3.1 ± 0.5 h. Seventeen patients were extubated to PPV via tracheostomy in the OR. Two patients were extubated to NPPV on postoperative day (POD) 1. Mean transition time to home ventilator or NPPV was 3.0 ± 2.2 days, and mean hospital stay was 5.0 ± 2.1 days. One patient premedicated without ventilatory support developed hypoxemia and hypoventilation. Ten patients (52%) had intraoperative events such as bradycardia, hypotension, significant hypoxemia, and bronchospasm. Fifteen patients had postoperative events. Hypoxemia, pneumonia, and atelectasis accounted for most of perioperative complications. One patient experienced seizure on POD 2 due to hypercarbia.

Conclusion Patients with CCHS are vulnerable to the cardiorespiratory effects of sedative and anesthetic agents. Therefore, they require vigilant monitoring and optimal ventilatory support in the perioperative period.

Keywords Congenital central hypoventilation syndrome · Perioperative · Intraoperative · Anesthesia complications · Ventilation

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Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder characterized by failure of automatic control of breathing [1]. CCHS is typically diagnosed in infancy and persists as a lifelong disorder as there is no known cure. The disease-defining gene mutation for CCHS involves the paired-like homeobox 2B (PHOX2B) gene, which is involved in neural crest cell migration and autonomic nervous system development [1–3]. Affected patients most commonly have a polyalanine repeat expansion mutation (PARM), with longer expansions generally associated with a more severe phenotype. Less than 10% of patients have nonpolyalanine repeat mutation (NPARM), which is

also usually found in patients with more severe manifestations of the disease [1, 4]

CCHS is characterized by severe hypoventilation during sleep that may extend to wakefulness. Affected patients can become hypoxemic and hypercarbic because they lack the necessary ventilatory responses to overcome these challenges [1, 5]. Therefore, patients with CCHS must rely on lifelong ventilatory support either during sleep only or 24 h per day to maintain adequate ventilation [1, 6–8]. Ventilatory support modalities include positive pressure ventilation (PPV) via tracheostomy, noninvasive positive pressure ventilation (NPPV), negative pressure ventilators, and diaphragm pacing (DP) [1, 7–14]. DP, in particular, allows patients requiring full-time ventilator support more independence during the day, while those who are ventilator-dependent only during sleep have the potential for decannulation of their tracheostomy [14, 15]

Several case reports have shown that patients with CCHS are particularly sensitive to neurodepressant medications [16–18]. Mahfouz et al. described an asymptomatic 6-year-old child who could not be extubated following general anesthesia for a dental procedure who was subsequently diagnosed with CCHS. In this case, the child was noted to breathe comfortably without overt respiratory distress despite pCO_2 of 112 mmHg [16]. Recently, we reported a case of a 52-year-old woman with history of prolonged recovery from anesthesia and an elevated serum bicarbonate of 45 meql/L who shared the same PHOX2B gene mutation as her child [18]. These cases suggest risk for vulnerability during the perioperative period. However, aside from case reports, there are limited published data on the management and outcomes of patients with CCHS undergoing general anesthesia [19–22].

The objective of this study was to describe the perioperative outcomes of patients with CCHS undergoing a diaphragm pacer-related procedure under general anesthesia. We chose this procedure to reduce confounders. Because it is an elective procedure, patients must be at their optimal healthy baseline at the time of surgery.

Methods

We conducted a historical cohort study of all patients with CCHS who underwent a primary implantation of bilateral phrenic nerve electrodes for diaphragm pacing at the Children's Hospital Los Angeles (CHLA) between January 2000 and May 2016. Patients with genetically confirmed diagnosis of CCHS were included. Charts were reviewed for demographics, *PHOX2B* genotype, usual need for ventilatory support, type of ventilatory support, associated medical conditions, type and dosage of anesthesia medications administered, and the pre-, intra-, and postoperative course of each procedure. Descriptive statistics were used to describe the study population.

The study was approved by the Children's Hospital Los Angeles Institutional Review Board.

Results

Patient characteristics

Of the 19 patients who underwent primary phrenic nerve pacer implantations, 11 were female (58%). The mean age at surgery was 8.6 ± 5.8 years (range 3–23 years) with a mean BMI of 18.6 ± 4.9 kg/m^2. One patient was obese based on cutoffs by the World Health Organization of BMI of ≥ 30 kg/m^2. PHOX2*B* gene mutation was confirmed in all patients. Nine patients had 20/25 polyalanine repeat expansion mutation (PARM), 2 patients had 20/26 PARM, seven had a 20/27 PARM, and one had a novel point p.P82L mutation. Seven patients had autonomic nervous system dysfunction (ANS) manifestations in their history such as Hirschsprung's disease, gastroesophageal reflux disease, cardiac pacemaker dependence for bradyarrhythmia, and strabismus. Four patients had feeding gastrostomies. Other associated conditions are listed in Table 1. Six patients had more than 1 associated ANS dysfunction and/or medical condition.

Each stage of anesthesia is described along with their related outcomes.

Table 1 Comorbidities for patients undergoing primary diaphragm pacer implantation

Comorbidity	*n*
ANS dysfunction	
Cardiac pacemaker dependence	3
Gastroesophageal reflux disease	4
Hirschsprung's disease	3
Strabismus	2
Neurologic/psychiatric	
Seizure disorder	2
Neurodevelopmental delay	2
Attention deficit hyperactivity disorder	1
Other	
Asthma	1
Conductive hearing loss	1
Juvenile rheumatoid arthritis	1

Preoperative considerations

Mode of ventilation

At the time of diaphragm pacer implantation, 17 patients were receiving ventilatory support during sleep only, while the remaining two patients received 24-h ventilatory support. Of the 17 patients receiving sleep-only ventilatory support, 14 were using PPV via tracheostomy, and 3 by NPPV via mask. One of the 3 patients ventilated noninvasively still had tracheostomy that was capped 24 h/day. Both patients on 24-h ventilatory support used PPV via tracheostomy as their primary mode of ventilatory assistance. The two patients, who did not have a tracheostomy in place at the time of diaphragm pacer implantation, were on NPPV prior to the operation.

Preoperatively, two patients received premedication in the form of midazolam.

Events

One of the two patients given preoperative sedation was not placed on mechanical ventilatory assistance and experienced profound sedation and hypoventilation with oxygen saturation down to 78% (Table 2). Hand bag-to-trach ventilatory support was instituted, and she was subsequently placed on her home ventilator until she went to the operating room. No long-term sequelae were apparent.

Intraoperative considerations

Anesthesia

All 19 patients were intubated endotracheally and received general anesthesia for the surgery. We found a variation in anesthetic management based on individual anesthesiologist's preference. Six patients (32%) with tracheostomy were induced via inhalation route alone, eleven (58%) combined inhalation via tracheostomy and an IV route, and two (11%) intravenously with propofol only. To facilitate endotracheal intubation, seven patients received a neuromuscular blocker in the form of vecuronium or rocuronium (5) or succinylcholine (2). These medications were allowed to wear off during the procedure to enable testing of the diaphragm pacer system intraoperatively. The other 12 patients were intubated by deepening the anesthetic plane using a combination of sevoflurane, propofol, and fentanyl. Anesthesia was maintained with sevoflurane in 16/19 patients and total intravenous anesthesia in three. This included propofol and remifentanil infusions in 2 and propofol, dexmedetomidine, and remifentanil infusion in one. Fifteen patients received intraoperative fentanyl and four patients received morphine towards the end of their procedure.

Diaphragm pacers were implanted thoracoscopically as protocol in our center [23, 24]. The surgery required one lung ventilation whereby the ipsilateral lung is deflated for the surgical placement of the phrenic nerve electrodes. The mean surgery duration was 3.1 ± 0.5 h (range 2.4–4.1 h).

Table 2 Perioperative events for patients undergoing primary diaphragm pacer implantation

Event	*n*	*PHOX2B* Genotype (n)
Preoperative events		
Hypoventilation with sedation	1	20/26 PARM
Intraoperative events		20/25 PARM (3); 20/26 PARM (1); 20/27 PARM (6)
Bradycardia	2	
Hypotension	2	
Hypoxemia with 1 lung ventilation	5	
Bronchospasm	2	
Postoperative events		20/25 PARM (8); 20/26 PARM (2); 20/27 PARM (4); NPARM (1)
Seizures	1	
Atelectasis	12	
Pneumonia	5	
Pneumothorax	4	
Tachycardia	4	
Fever	2	
Urinary retention	3	
Nausea/vomiting	2	
Lactic acidosis	1	

Events

Out of the 19 operations, intraoperative events were noted in 10 (53%). Two patients had intraoperative bradycardia (11%). One of the patients had brief bradycardia to less than 30 bpm that responded to IV atropine. In addition, this patient received chest compressions for the low heart rate but did not have asystole or hypotension. The other patient had bradycardia to 34 bpm, relieved with IV atropine without the requirement for cardiopulmonary resuscitation. One patient was noted to be hypotensive that occurred within 5 min of anesthesia induction but resolved with placement in Trendelenburg position and intramuscular atropine. Five patients had hypoxemia with the lowest SpO2 of 50% and 2 patients had bronchospasm (Table 2).

Postoperative considerations

All patients continued to receive positive pressure ventilation postoperatively. Seventeen patients were extubated to tracheostomy in the OR. The duration of intubation was 4.0 ± 0.6 h (range 3.2–5.3 h). The two remaining patients, who were previously on NPPV via mask, went to the PICU intubated and were extubated to NPPV on postoperative day 1. The patient on NPPV by mask at home but had tracheostomy capped full time was transitioned to a portable ventilator. Mean time for transition to portable ventilator was 3.0 ± 2.2 days (range 1–9 days), and mean hospital stay was 5.0 ± 2.1 days (range 3–12 days).

Events

Postoperative events were noted in 15 diaphragm implantation procedures (79%). One patient experienced a 2-min generalized tonic–clonic seizure on postoperative day two (5%), attributed to hypoventilation with rising CO2 over course of few hours up to 85 mmHg on end-tidal CO_2 monitoring. Seizure resolved with lorazepam during which the patient was hand-bagged with normalization of gas exchange. Twelve patients were found to have atelectasis (63%), with five treated with antibiotics for pneumonia. Four patients had pneumothoraces related to the surgery and had chest tubes for up to 5 days. Four patients had recorded episodes of tachycardia. Other noted postoperative events included fever (2), urinary retention (3), nausea and vomiting (2), and mild lactic acidosis in one patient (Table 2). Eight of the 12 patients (67%) who developed atelectasis were transitioned to their home ventilator/NPPV within 3 days of surgery and only 1 of the 12 patients was transitioned to home ventilator after 1 week of surgery. Three of these 12 patients were hospitalized for ≥ 7 days.

Discussion

Our study showed that a significant proportion of patients with CCHS have anesthetic complications pre-, intra-, and/or post primary diaphragm pacer implantation surgery under general anesthesia. To our knowledge, there are limited data that describe an optimal anesthetic approach for managing these patients.

Cardiovascular presentations of CCHS include alterations in autonomic function including decreased heart rate variability, bradycardia, and transient asystole [24–28]. Woo et al. described bouts of bradycardia and tachycardia that can occur in CCHS patients, unrelated to central hypoventilation [24]. This autonomic instability may be correlated with the intraoperative bradycardia that was seen in a subset of our patients.

During the thoracoscopic placement of the phrenic nerve electrodes, the lungs are deflated sequentially, putting patients at risk for atelectasis and pneumonia. We found atelectasis in 2/3 of our cohort with 24% requiring treatment for pneumonia. Ballard et al. found atelectasis in 3 of 14 patients (21%) undergoing diaphragm pacers implantation surgery [19]. Our findings highlight the significance of airway clearance and ventilatory support to mitigate these complications. In our center, we optimize airway clearance therapies with bronchodilator and chest physiotherapy in the post-op period to minimize this risk. In those with large tracheostomy stoma, the tracheostomy tube is upsized or cuffed tracheostomy tube is temporarily used in the immediate post-op period to improve ventilation.

During the surgery, anesthesiologists need to be aware that neuromuscular blocking agents should not be used because the diaphragm pacer system is tested several times intraoperatively. When using these agents to facilitate intubation, the agents should be short acting or allowed to wear off by the time testing is performed. One patient had profound hypoventilation after premedication highlighting the importance of ensuring that all patients with CCHS receive adequate assisted ventilation and gas exchange monitoring if receiving premedication since they lack subjective and objective responses to hypoxia or hypercapnia. Therefore, these patients will not demonstrate respiratory distress, tachypnea, or retractions in response to hypercarbia or hypoxemia. Hence, it is imperative that healthcare team involved in their perioperative care must be aware of the importance of close monitoring and ventilatory support during this vulnerable period. The importance of vigilant monitoring and need for mechanical ventilation extends to the post-op period when patients are receiving sedating, pain, or other CNS depressant medications. In patients with CCHS, the most

Table 3 Approach to patients undergoing phrenic nerve electrode implantation surgery for diaphragm pacing

Preoperative
- Connect patient to home ventilator or NPPV prior to administration of pre-operative sedative medications
- Continuous pulse oximetry monitoring and PETCO2 monitoring if available
- Goal: Spo2 ≥ 95% and PETco2 ≤ 40 torr

Intraoperative
- Adjust ventilatory support to always achieve Spo2 ≥ 95% and PETco2 ≤ 45 torr
- No neuromuscular blocking agents during surgery; if needed for intubation, use short acting agent, or allowed to wear off by the time testing of diaphragm pacer system is performed
- IV Vancomycin—1st dose to prevent infection

Postoperative
- Admit from the OR to the intensive care unit for close monitoring
- Adjust ventilatory support to achieve Spo2 ≥ 95% and PETco2 ≤ 40 torr
- Continue Vancomycin 15 mg/kg/dose q8h for at least 3 doses
- Beginning immediately after surgery, aerosolized bronchodilator therapy and chest physiotherapy to decrease the risk of postoperative atelectasis and pneumonia
- Upsize the tracheostomy tube or temporarily use cuffed tracheostomy tube for those with large tracheostomy stoma
- In the event of unexplained problem (seizure, lethargy, etc.), patient is hyperventilated with supplemental oxygen until the source of the problem can be identified
- Chest tube management per surgery
- Transition from hospital ventilator to home ventilator or NPPV by mask when stable
- Diaphragm pacers are not used during the hospitalization. Patient is discharged to home when stable using pre-hospitalization ventilatory support

common problem is inadequate ventilation whether they are awake or asleep; therefore, when problems arise (i.e., seizures, lethargy), the first step should be to provide optimal ventilatory support. At the authors' center, patients are stabilized with hyperventilation and supplemental oxygen until the source of the problem can be identified. Because of CCHS, the etiology of any such problem is likely to be hypoventilation until proven otherwise and a brief period of hyperventilation will not be harmful, but may be life-saving. Our approach in caring for patients with CCHS undergoing phrenic nerve electrode implantation surgery for diaphragm pacing is summarized in Table 3.

Our study has some limitations in that being retrospective, some data points are not available and not all events that occurred may have been captured. Furthermore, the numbers are too small to run a subgroup analysis to determine the relationship of the occurrence of events and the *PHOX2B* genotype.

Given that patients with CCHS undergoing primary diaphragm pacer implantation surgery are at their optimal healthy baseline, we chose to study this group to examine their perioperative outcomes as related to anesthesia to reduce confounders. We propose that our findings on the outcomes from the effect of anesthesia may occur in any patient with CCHS receiving sedation and anesthesia for any surgeries or procedures. Our study showed that all patients experienced at least one anesthetic complication before, during, or after a diaphragm pacer implantation surgery. We speculate that these complications were caused or exacerbated by absent ventilatory responses or autonomic dysfunction. Therefore, it is vital that the healthcare team is cognizant of the increased risks in patients with CCHS, the crucial role of appropriate monitoring to prevent hypoxia and/or hypoventilation, and the delivery of adequate ventilatory support in the pre-, intra-, and postoperative periods.

Author contribution Gloria Y. Chang, Tate Salazar, Abhishek Karnwal, Sheila S. Kun, Josephine Ellashek, Cathy Shin, J. Gordon McComb, Thomas G. Keens, and Iris A. Perez contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Gloria Y. Chang, Tate Salazar, Abhishek Karnwal, Sheila S. Kun, Josephine Ellashek, Cathy Shin, J. Gordon McComb, Thomas G. Keens, and Iris A. Perez. The first draft of the manuscript was written by Gloria Y. Chang, Tate Salazar, Thomas G. Keens, and Iris A. Perez, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the findings of the study are not openly available due to patient confidentiality.

Code availability Not applicable.

Declarations

Ethics approval The study was approved by the Institutional Review Board (IRB) of Children's Hospital Los Angeles (IRB# CHLA-16–00249).

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals Not applicable.

References

1. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I et al (2010) An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med 181:626–644. https://doi.org/10.1164/rccm.200807-1069ST
2. Amiel J, Laudier B, Attié-Bitach T et al (2003) Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet 33:459–461. https://doi.org/10.1038/ng1130
3. Silvestri JM, Chen ML, Weese-Mayer DE et al (2002) Idiopathic congenital central hypoventilation syndrome: the next generation. Am J Med Genet 112:46–50. https://doi.org/10.1002/ajmg.10819
4. Matera I, Bachetti T, Puppo F et al (2004) PHOX2B mutations and polyalanine expansions correlate with the severity of the respiratory phenotype and associated symptoms in both congenital and late onset Central Hypoventilation syndrome. J Med Genet 41:373–380
5. Paton JY, Swaminathan S, Sargent CW, Keens TG (1989) Hypoxic and hypercapnic ventilatory responses in awake children with congenital central hypoventilation syndrome. Am Rev Respir Dis 140:368–372. https://doi.org/10.1164/ajrccm/140.2.368
6. Chen ML, Keens TG (2004) Congenital central hypoventilation syndrome: not just another rare disorder. Paediatr Respir Rev 5:182–189. https://doi.org/10.1016/j.prrv.2004.04.009
7. Maloney MA, Kun SS, Keens TG, Perez IA (2018) Congenital central hypoventilation syndrome: diagnosis and management. Expert Rev Respir Med 12:283–292. https://doi.org/10.1080/17476348.2018.1445970
8. Bishara J, Keens TG, Perez IA (2018) The genetics of congenital central hypoventilation syndrome: clinical implications. Appl Clin Genet 11:135–144. https://doi.org/10.2147/TACG.S140629
9. Vagiakis E, Koutsourelakis I, Perraki E et al (2010) Average volume-assured pressure support in a 16-year-old girl with congenital central hypoventilation syndrome. J Clin Sleep Med 6:609–612
10. Kerbl R, Litscher H, Grubbauer HM et al (1996) Congenital central hypoventilation syndrome (Ondine's curse syndrome) in two siblings: delayed diagnosis and successful noninvasive treatment. Eur J Pediatr 155:977–980
11. Tibballs J, Henning RD (2003) Noninvasive ventilatory strategies in the management of a newborn infant and three children with congenital central hypoventilation syndrome. Pediatr Pulmonol 36:544–548. https://doi.org/10.1002/ppul.10392
12. Hartmann H, Jawad MH, Noyes J et al (1994) Negative extrathoracic pressure ventilation in central hypoventilation syndrome. Arch Dis Child 70:418–423
13. Chen ML, Tablizo MA, Kun S, Keens TG (2005) Diaphragm pacers as a treatment for congenital central hypoventilation syndrome. Expert Rev Med Devices 2:577–585. https://doi.org/10.1586/17434440.2.5.577
14. Diep B, Wang A, Kun S et al (2015) Diaphragm pacing without tracheostomy in congenital central hypoventilation syndrome patients. Respiration 89:534–538. https://doi.org/10.1159/000381401
15. 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. J Clin Sleep Med 14:261–264. https://doi.org/10.5664/jcsm.6948
16. Mahfouz AKM, Rashid M, Khan MS, Reddy P (2011) Late onset congenital central hypoventilation syndrome after exposure to general anesthesia. Can J Anesth. https://doi.org/10.1007/s12630-011-9590-7
17. Basu SM, Chung FF, AbdelHakim SF, Wong J (2017) Anesthetic considerations for patients with congenital central hypoventilation syndrome: a systematic review of the literature. Anesth Analg 124:169–178. https://doi.org/10.1213/ANE.0000000000001470
18. Kasi AS, Kun SS, Keens TG, Perez IA (2018) Adult with PHOX2B mutation and late-onset congenital central hypoventilation syndrome. J Clin Sleep Med 14:2079–2081. https://doi.org/10.5664/jcsm.7542
19. Ballard HA, Leavitt OS, Chin AC et al (2018) Perioperative anesthetic management of children with congenital central hypoventilation syndrome and rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation undergoing thoracoscopic phrenic nerve-diaphragm pacemaker. Paediatr Anaesth 28:963–973. https://doi.org/10.1111/pan.13475
20. Wiesel S, Fox GS (1990) Anaesthesia for a patient with central alveolar hypoventilation syndrome (Ondine's curse). Can J Anaesth 37:122–126. https://doi.org/10.1007/BF03007492
21. Ishibashi H, Umezawa K, Hayashi S, Shibutani K (2004) Anesthetic management of a child with congenital central hypoventilation syndrome (CCHS, Ondine's curse) for dental treatment. Anesth Prog 51:102–104
22. Shaul DB, Danielson PD, McComb JG, Keens TG (2002) Thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing in children. J Pediatr Surg 37:974–8. discussion 974-8
23. Nicholson KJ, Nosanov LB, Bowen KA et al (2015) Thoracoscopic placement of phrenic nerve pacers for diaphragm pacing in congenital central hypoventilation syndrome. J Pediatr Surg 50:78–81. https://doi.org/10.1016/j.jpedsurg.2014.10.002
24. Woo MS, Woo MA, Gozal D et al (1992) Heart rate variability in congenital central hypoventilation syndrome. Pediatr Res 31:291–296. https://doi.org/10.1203/00006450-199203000-00020
25. Trang H, Girard A, Laude D, Elghozi J-L (2005) Short-term blood pressure and heart rate variability in congenital central hypoventilation syndrome (Ondine's curse). Clin Sci (Lond) 108:225–230. https://doi.org/10.1042/CS20040282
26. Silvestri JM, Hanna BD, Volgman AS et al (2000) Cardiac rhythm disturbances among children with idiopathic congenital central hypoventilation syndrome. Pediatr Pulmonol 29:351–358
27. Gronli JO, Santucci BA, Leurgans SE et al (2008) Congenital central hypoventilation syndrome: PHOX2B genotype determines risk for sudden death. Pediatr Pulmonol 43:77–86. https://doi.org/10.1002/ppul.20744
28. Laifman E, Keens TG, Bar-Cohen Y, Perez IA (2020) Life-threatening cardiac arrhythmias in congenital central hypoventilation syndrome. Eur J Pediatr 179. https://doi.org/10.1007/s00431-019-03568-5