Section 11: Central hypoventilation, congenital and acquired

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Central hypoventilation can arise either as a primary disorder of the central respiratory nuclei (either genetic or acquired) or as an adaptive phenomena due to chronic respiratory or respiratory motor insufficiency (as in end-stage chronic lung disease or neuromotor disease). The latter will be discussed in the relevant sections. This section deals with congenital central hypoventilation syndrome (CCHS). For a more detailed overall review of CCHS, the reader is referred to a recent American Thoracic Society (ATS) Statement on CCHS.1

Introduction

Central hypoventilation can arise either as a primary disorder of the central respiratory nuclei (either genetic or acquired) or as an adaptive phenomena due to chronic respiratory or respiratory motor insufficiency (as in end-stage chronic lung disease or neuromotor disease). The latter will be discussed in the relevant sections. This section deals with congenital central hypoventilation syndrome (CCHS). For a more detailed overall review of CCHS, the reader is referred to a recent American Thoracic Society (ATS) Statement on CCHS.1

Literature review: Methodology

Searches were conducted looking for publications on (1) congenital central hypoventilation syndrome and (2) central apnea syndromes. We aimed at identifying all studies published in English. MEDLINE databases (1966 to August 24, 2015) were searched. As well, reference lists from identified publications were hand searched in order to add any missed studies. We also searched the web sites of large associations of physicians and health professionals in the fields of respiratory medicine, intensive care, nursing and respiratory therapy for reviews, consensus statements and clinical practice guidelines.

Results

We initially retrieved 350 English-language publications that were relevant to our inclusion criteria and dealing with congenital central hypoventilation syndrome. Publications dealing solely with adult populations were eliminated. We were then left with 224 publications dealing with congenital central hypoventilation syndrome. These papers were narrowed to those with a focus on the respiratory management of CCHS. A separate search was performed looking for syndromes associated with central apnea. Seventeen references were used from this search.

Discussion

Congenital central hypoventilation syndrome

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder characterized by ventilatory insensitivity to hypercapnia and hypoxemia during sleep and/or wakefulness. Hypoventilation is most pronounced during nonrapid eye movement sleep, during which breathing is primarily controlled by the autonomic nervous system;2 this is not always the case, however, and CCHS can present in infancy, childhood or adulthood.

There are no randomized trials examining best ventilatory practices, though management of CCHS has been described by experts in the field.1,3–6 Chronic, lifelong ventilatory support at home is the treatment of choice for these patients because children with CCHS do not outgrow their symptoms. Current pharmacologic treatments are ineffective, and oxygen therapy corrects the hypoxemia but not the ventilatory derangement.2,7–10

Children and infants with CCHS can present with varying degrees of severity; in less severe cases, careful ventilatory management is still recommended to improve outcomes with respect to the sequelae of recurrent hypoxemia and hypercarbia.6,10,11 These sequelae include adverse neurologic outcomes, developmental problems, pulmonary hypertension with right-sided heart failure and death.1,12–18 Although there are a few reports of long-term survival without support,19 this is not recommended given the potential for these serious sequelae. This is further borne out by patients with late diagnosis of CCHS in whom right-sided heart dysfunction, intellectual compromise and seizures have been reported.16,20,21 Thus all patients with CCHS should be supported to ensure optimal oxygenation and ventilation.

There are various options available in terms of the type of support. Options include positive pressure ventilation via tracheostomy, noninvasive positive pressure ventilation (NiPPV), diaphragm pacing and negative pressure ventilation. To the authors’ knowledge, there are no comparative trials examining the relative advantages and disadvantages of...
these differing modes of ventilation. Thus, until definitive studies occur, treatment should be optimized for each individual in order to achieve normal ventilation and oxygenation as assessed by standard polysomnography. General recommendations can be derived from the literature and clinical experience, which are echoed by the recent ATS guidelines.\(^1\)

NIPPV can be delivered via a nasal or oronasal interface using a bilevel positive airway pressure ventilator. Full face-masks in young children are usually not used given the risks of aspiration with emesis. NIPPV is generally best suited to older children or adults with less severe CCHS cases requiring solely nocturnal ventilator support. The advantage of NIPPV is that it is a tracheostomy is not required. This leads to a considerable reduction in the training, education, expense and nursing/home support required. The disadvantages of NIPPV include the potential for mid-face hypoplasia and skin breakdown, as well as less security in the delivery of ventilatory support.\(^2\)

For all infants and those with more severe CCHS cases, invasive ventilation (nocturnal or both day and night) is recommended via a tracheostomy. This is often a cause of great anxiety for parents and some healthcare professionals as they weigh the certainty of a tracheostomy with the future ‘downstream’ risks of hypoxemia and hypercarbia.\(^22\)–\(^24\) There are reports of some centers managing CCHS with nocturnal NIV in infants from a very young age with success.\(^25\) For infants with CCHS, with regards to NIV, there will be significant challenges with mask fit, and also with ensuring oxygenation and ventilation can be optimally managed. Ideally, in these patients, home monitoring will be performed, including oxygen saturation and transthoracic carbon dioxide (\(\text{CO}_2\)).\(^26\) Annual photos of the face and consultation with plastic surgery should be considered as well. The current ATS guidelines do state that in the first “several” years of life, a tracheostomy is the recommended way to ventilate children with CCHS.\(^1\) A tracheostomy provides a secure airway, guarantees ventilation and can help ensure that normoxia for optimal brain growth and development is met in the early years.\(^2\) Support can be given for 24 hours a day if needed, including while feeding. Risks associated with a tracheostomy include infection, bleeding and impaired airway clearance. There may be an effect on speech, and a referral to a speech language pathologist is recommended. The patient and family will require more intensive family education and support for ventilation via tracheostomy, as compared to other modalities. As the child ages, transition to NIV is feasible.\(^1,27\)

Phrenic nerve stimulation/diaphragm pacing is a potential option for CCHS.\(^6,10,28–32\) This form of support is best suited to older patients who require more than just nocturnal support but who would benefit from the freedom of not having a ventilator attached during the day. Pacing allows this mobility by triggering respiratory activity without the need for positive pressure ventilation. Patients usually require a tracheostomy to prevent upper airway obstruction caused by the absence of laryngeal and pharyngeal dilator muscle activation during paced breaths.\(^22,32\) However, decannulation is feasible. In addition, patients require bilateral phrenic nerve pacing, as opposed to unilateral, to ensure adequate ventilation, given the compliant chest wall and children’s higher metabolic rates.\(^32\) Diaphragm pacing is used up to 12 hours a day in the pediatric population\(^24\) in order to reduce the risk of phrenic nerve damage secondary to traction as well as nerve burn out. Given the surgical and technical complexities required to achieve optional ventilation while minimizing risks, this form of support requires a center with experience in diaphragm pacing. Currently there are only 3 centers in Canada that follow pediatric patients with diaphragm pacing: McGill (Montreal), McMaster (Hamilton) and BC Children’s Hospital (Vancouver).

Negative pressure ventilators have also been used with some success. These ventilators provide a negative pressure outside the chest and abdomen in order to expand the chest. The bulk of the machine makes it cumbersome, difficult to sleep in and nonportable (there are no batteries currently available). Passive motion of lower extremities has been shown to increase ventilation but there is not enough evidence to support this as a reliable therapy in these patients.\(^2\)

An annual polysomnography to evaluate ventilator support settings is recommended for older children, and for children less than 3 years of age, a sleep study every 6 months is recommended. The goals for end-tidal carbon dioxide should be 30–50 mmHg (ideally 35–40 mmHg) and oxygen saturations greater than 95%.

Although CCHS is a lifelong condition, the modality of support required may change over time. It is not unexpected for infants to eventually be decannulated and use nocturnal NIPPV instead of invasive support via tracheostomy.\(^27,36\) The age for this change is variable and will depend on patient factors, as well as the availability of appropriate equipment and support. In addition, patients initially managed with NIPPV have over time transitioned to invasive support.

As these patients have reduced ability to sense and respond to hypercarbia and hypoxemia, oxygen saturation should be monitored while asleep and also periodically during the day during special circumstances (such as an infection) while at home. \(\text{CO}_2\) monitoring at home would clearly be of benefit. However, to date in Canada, no product has been endorsed by government or a medical establishment for this purpose. Oxygen therapy in the home should be avoided in isolation as this has the potential to mask hypventilation in the absence of \(\text{CO}_2\) monitoring.

**Acquired central hypoventilation syndromes**

If the history is suggestive and/or the PHOX2B genetic studies do not reveal a mutation, then other diagnoses leading to central hypoventilation should be considered. A premature infant may have non-CCHS related central apneas that...
are developmental in nature. Acquired causes of central hypoventilation may also include brainstem compression (Chiari malformation), trauma, medication, tumors, infection or cerebrovascular accidents. A brainstem MRI should be performed as part of this workup. In addition to CCHS, other potential congenital conditions associated with central hypoventilation include familial dysautonomia, Mobius syndrome, Pitt Hopkins syndrome, Prader-Willi syndrome, skeletal dysplasia, Joubert syndrome, achondroplasia, Athabascan brainstem dysgenesis syndrome and other inborn errors of metabolism.

Management of acquired central hypoventilation is similar to hypoventilation in CCHS, if the underlying disorder cannot be treated or corrected. The same treatment options are available (including tracheostomy, NiPPV and diaphragm pacing). Choice of support should be individualized to the patient and condition. Although in general, aiming for saturation greater than 95% and end tidal CO2 ranging from 35 to 45 mmHg may be desirable, these goals clearly may be modified by other factors including prognosis and comorbidities.

**Conclusion**

The aim of therapy of central hypoventilation in children should be to support ventilation in order to minimize sequelae of hypoxemia and hypercarbia. Options for support include positive pressure ventilation via tracheostomy, NiPPV or diaphragm pacing. Although there is a preference for minimizing the invasiveness of interventions, support should be individualized to each patient. Generally, younger patients require more invasive support. Patients with CCHS do not outgrow their need for support; it may be possible, however, to reduce the invasiveness of the support as the patient ages.

**Research questions**

1. What is the optimal method of ventilatory support for children with central hypoventilation syndromes? And how does this change with age and developmental level?
2. What are the optimal physiologic targets (CO2, O2) for ventilatory support?
3. How often should children with central hypoventilation syndromes have a PSG?
4. How should children with central hypoventilation syndromes be monitored in the home environment (oxygen saturation monitor alone or in combination with CO2 monitoring)?

**Recommendations for long-term mechanical ventilation at home in children with central hypoventilation, congenital and acquired**

1. Patients with congenital central hypoventilation syndrome should receive lifelong ventilatory support in order to avoid hypoxemia and hypercarbia. (Grade 1C)
2. Ventilation should be optimized to maintain as close to normal gas exchange during wakefulness and sleep. The ideal target levels for end tidal/transcutaneous CO2 are 35–40 mmHg and oxygen saturations greater than 95% during sleep. (Grade 1C)
3. Children with congenital central hypoventilation syndrome should undergo formal titration to optimize gas exchange (as defined in criteria in no. 2 above) at least annually by nocturnal PSG and twice a year for those under 3 years old. (Grade 1C).
4. Children with other central hypoventilation syndromes should undergo formal titration to optimize gas exchange (as defined in criteria in no. 2 above) at least annually by nocturnal PSG. (Grade 1C)
5. Children with congenital central hypoventilation syndromes should be discharged home with a portable oximeter to monitor oxygen saturations. (Grade 2C)
6. The mode (positive pressure ventilation via tracheostomy, NIV, diaphragm pacing) and degree of ventilatory support should be individualized for each patient. (Grade 1C)

**References**


