Chapter 1
Chronic Ventilator Support in Children: Why, Who, and When

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Introduction

Until around 25 years ago, there were limited options for long-term ventilation of children, requiring either cumbersome equipment ("iron lung") or invasive ventilation (via a tracheostomy). Consequently the majority of children on long-term ventilation were cared for either in general hospitals or specific long-term ventilation facilities. With improving technology, particularly in the delivery of noninvasive ventilation [2], there has been a marked increase in the number of children being placed on long-term ventilation [2–5], to the point that it is currently regarded as a standard of care for children with conditions that were previously thought to be inevitably fatal, the majority of whom are now cared for in their home. Despite its widespread use, however, there remains very little comparative literature on the optimal indications and patient selection process, optimal timing, or most effective process for initiation of chronic ventilation in children. Moreover most of the available evidence is either from adult populations or mixed populations of adults and children with, unfortunately, a paucity of pediatric specific data. This is reflected by the marked variability in frequency, types of patients, and differing modes of ventilation reported between different centers [1, 6, 7], with ongoing evolution in the conditions deemed appropriate for long-term ventilation [3, 6, 8, 9].

Most long-term ventilation programs have developed their own criteria and protocols for the initiation of long-term ventilation, based largely on logic and empiric experience. Although these protocols are generally similar, being based on similar experience and therapeutic goals, there is still a lack of agreement as to precisely

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who would benefit from long-term home ventilation, or exactly when in the child's disease process it should be initiated [1]. Ideally we would have clear evidence to guide us in our approach to initiation of home ventilation. What literature there is, however, generally describes which individuals were placed on long-term ventilation, how ventilation was initiated, and some outcome data, the majority of this data, as noted, covering populations of all ages. Given that children placed on long-term ventilation, by definition, are commonly facing life-limiting illnesses and that caring for these children has a major impact on family functioning and family finances, the relative absence of objective data providing support for these protocols is a significant deficit of our knowledge.

In order to address which children require chronic ventilator support, it is easiest to first consider the "why," the rationale for placing a child on long-term ventilator support.

Why?

When considering the indications for initiating chronic ventilation, the mode of ventilation required or available has a significant impact on the decision-making process. Simplistically there are two options for delivering chronic ventilation:

1. Noninvasive positive pressure ventilation (NIPPV) by an oral or nasal interface such as a mask, or negative pressure ventilation such as with a cuirass (though this commonly also requires a tracheotomy).
2. Invasive positive pressure ventilation by a tracheotomy.

   Phrenic nerve pacing is a third option for selected patients. It is usually regarded as invasive in that it requires surgical implantation, with many children continuing to require tracheostomy post insertion.

As will be discussed in Chap. 2 and Chap. 3, these different methodologies have their particular advantages and disadvantages. Compared to invasive ventilation, noninvasive ventilation is, however, more readily discontinued in that it simply requires placement of an interface, such as nasal or full face mask. It is therefore amenable to use as a "therapeutic trial," since it can be easily discontinued if found to be ineffective, poorly tolerated, or actually detrimental to the child's respiratory status or quality of life. In a neurologically intact child, with milder degrees of hypoventilation such that ventilatory support is not required for survival, even relatively young children can therefore themselves decide when or whether to use the device. Invasive ventilation, in contrast, not only requires surgical intervention but also, due to the increased complexity of the equipment and the level of care required, necessitates a significantly greater family commitment, both in terms of increased risks associated with initiation and greater caregiver time and education to allow for safe care of the child at home. At the more severe end of the clinical spectrum, however, where patients are dependent on ventilatory support for survival, both patients

and family need to understand the rationale for assisted ventilation, whether invasive or noninvasive, and the important role it plays in the care plan of the child.

A variety of reasons exist for initiation of long-term ventilation in children:

1. Prolongation of life. A child with end-stage respiratory failure, as evidenced by persisting daytime hypercapnia, has limited life expectancy. This is therefore the simplest scenario in terms of justification and decision making, since, in the absence of a definitive treatment, long-term ventilation is the only option for continued survival (though assisted ventilation can be a component of palliative care, below). Ideally the patient (where appropriate) and their family will have had sufficient time and education to make an informed decision, in agreement with the child's medical team, as to whether initiation of chronic ventilation is an appropriate therapy for their child (Chap. 4). For example, parents of a neonate with profound hypoventilation as the presenting indicator of congenital central hypoventilation syndrome have little option other than invasive ventilation for their child's survival. In contrast, parents of a child with progressive neuromotor disease, such as spinal muscle atrophy, will hopefully have had sufficient time and counseling to decide in advance the appropriate therapeutic plan in order to delay or ameliorate the onset of overt hypoventilation.
2. Increased life expectancy. It is an oxymoron that a child in end-stage respiratory failure needs assisted ventilation to maintain life. There is good evidence, however, that initiating long-term ventilation earlier in the disease course can significantly improve life expectancy in selected populations. Perhaps the best evidence is in patients with progressive neuromotor disease. For example, with initiation of noninvasive ventilation, there has been almost a doubling in life expectancy of patients with Duchenne muscular dystrophy [10]. Although this is not randomized controlled data, the improvement in life expectancy is so striking, and reported by multiple centers [11–13], to believe that it is a consequence of the initiation of ventilation.
3. Improvement in quality of life. One common concern, and a reason for not initiating ventilation in patients with terminal illness, was the concern that this was merely "prolonging their suffering." It has, however, been realized that, although many patients perceive themselves as asymptomatic [14], not only does the resulting hypercapnia and hypoxemia produce significant symptoms in their own right, but the associated sleep fragmentation also causes significant symptoms, such as morning headaches, daytime somnolence, and generalized fatigue. Correcting these sequelae by initiating nocturnal ventilatory support, even if this were not to increase longevity, can result in significant improvements in quality of life and is sufficient to warrant its use in selected patients. Moreover it has been realized that individuals with progressive disease adapt to their medical condition, which becomes their "normal," for example, individuals with neuromotor disease.

   (a) Perceive their quality of life as being significantly better than either their parents or their medical team [15, 16].

(b) May actually see their ventilator in a positive light since, by improving their ventilation, they feel better and consequently perceive a resulting improved quality of life [17].

4. Treatment of hypoventilation.

(a) Nocturnal. Most children with progressive respiratory impairment will develop episodes of nocturnal hypoventilation years before they progress to daytime hypoventilation. Rapid eye movement sleep (REM) is classically associated with loss of skeletal muscle tone and hence loss of accessory muscles of respiration (though diaphragmatic function is preserved), whereas slow wave sleep (SWS or stage 3) is associated with loss of respiratory stimulation from the frontal cortex and hence relative loss of respiratory drive [18]. Consequently hypoventilation in diseases associated with loss of neuromotor function or respiratory muscle fatigue (end-stage pulmonary disease or disturbance of thoracic cage function) is typically worse during REM sleep, whereas patients with disorders of respiratory drive show worse sleep-disordered breathing in SWS. Although there may be a reduction in respect to respiratory function, the arousal response is commonly relatively well preserved and the sleep-related hypoventilation frequently triggers an arousal. This can happen repeatedly through the night, resulting in significant sleep fragmentation. Since, however, its onset is frequently insidious, many patients remain relatively asymptomatic [19, 20]. It is only with correction of the sleep-related hypoventilation that the patients may become aware of the severity of the symptoms arising secondary to their nocturnal hypoventilation and separate them from the symptoms associated with their underlying disease [21].

(b) Diurnal. As discussed above, once children with progressive disease become hypercapnic even while awake, they generally have a very limited life expectancy, with assisted ventilation (in the absence of any curative lesion) being their only hope for prolonged survival.

5. Improvement in clinical status.

(a) Lung clearance/cough. Efficient clearance of endobronchial matter requires an effective cough. Both progressive pulmonary and neuromotor diseases in particular are associated with reduced respiratory motor function resulting in reduced inspiratory (for generation of elastic recoil) and expiratory effort and hence reduced ability to generate a forceful expiration [22]. This adversely affects cough generation, with increasing risk of mucous plugging and opportunistic infections [22, 23]. A variety of techniques are therefore routinely employed to increase lung volumes [23]. Even in normal individuals, sleep suppresses cough [24], with the loss of skeletal muscle tone seen in REM sleep likely compounding the already elevated risk of mucous plugging and opportunistic infections. There is evidence to suggest that assisted nocturnal ventilation may reduce this risk [25, 26], presumably by increasing respiratory volume, as well as respiratory muscle rest [22], and hence improved cough effectiveness during sleep.

(b) Progressive loss of lung volume. In patients with progressive neuromotor disease, there is typically an associated, progressive restrictive defect, with progressive loss of lung volumes (see below). This is frequently due to associated reductions in tidal volume [27]. This appears to be ameliorated by the regular use of devices that induce maximal insufflation capacity (lung volume recruitment, or LVR) [27]. Whether a similar benefit can be obtained by using assisted ventilation to maintain lung volumes during sleep remains speculative in neuromotor disease, though this has been found in obesity hypoventilation syndrome [28].

6. Cost efficiency. Whatever healthcare system funding may be in place, caring for a child on chronic ventilation in an acute healthcare setting, such as a hospital, remains an extremely expensive treatment option. Although dependent upon a number of factors, most importantly being the level of externally funded supports provided in the community [1, 29], in general caring for a ventilator-dependent child at home versus in a long-term healthcare institution results in a significant cost saving to the healthcare system [30]. Discharging a patient home on chronic ventilation, however, although saving the healthcare system, transfers the costs of their care onto the family [1, 31]. There is marked variability worldwide in respect to the community resources provided to assist families in caring for these children. In even the most well-resourced healthcare system, however, a large proportion of the cost of these children's care within the home, not merely financial but also in terms of time and emotional investment, is borne by the family, especially the mothers [32]. At the same time, most parents, if given the option, would care for their child at home, with the necessity of ventilation usually adding little, if any, to the caregiver stress already created by the child's primary illness [33].
7. "Prophylaxis." Particularly in respect to noninvasive ventilation, which can be readily discontinued (above), it is attractive to believe that chronic ventilation might, if used early, be of value in ameliorating or at least delaying the progression of at least the respiratory component of a patient's disease. There is, however, unfortunately little data to support this hypothesis. In a 1994 study by Raphael et al. [34], a group of adolescents with Duchenne muscular dystrophy and forced vital capacities between 20 and 50 % of predicted but without daytime hypercapnia were randomly assigned to receive either "conventional treatment" or conventional treatment plus intermittent nocturnal noninvasive positive pressure ventilation (NIPPV) by nasal mask. The aim of the study was to prevent the progressive pulmonary restriction typically seen in these patients and therefore prolong survival. The authors, however, terminated this study early since NIPPV appeared to confirm no advantage on deterioration in pulmonary function, but paradoxically was associated with a fourfold higher death rate in the treatment population (eight patients versus two patients). In comparison, however, in a subsequent controlled study, 26 patients were randomized to receive either NIPPV or standard care without respiratory support [35]. Patients with NIPPV had improvements in nocturnal gas exchange and appeared to reduce the risk of acute deteriorations with daytime hypercapnia.

8. Parental and family wishes. Obviously in the ideal situation, there will be complete agreement between the parents, the child's medical team, and (where appropriate) the child themselves as to the necessity and appropriateness of initiation of long-term ventilation. Unfortunately this is frequently not the case, with relatively few families given adequate anticipatory information [36]. Despite our best efforts, and even with appropriate guidance, there inevitably will still be the (hopefully rare) situation where, even though the child's physicians may feel this is not in the child's best interests, the parents insist on initiating or continuing ventilation (usually, in this case, invasive). Generally, however the medical team may feel, the general rule in most Western healthcare systems is that the final decision rests with the family and (if able) the child (Chap. 4).
9. Temporizing device. Placing a child on chronic ventilation generally presupposes that the child is suffering from a chronic respiratory disease for which ongoing respiratory support is necessary. There are situations, however, where ventilator support (primarily noninvasive) might be used as a "temporizing" device.
    (a) Respiratory support. Ventilatory support in the home can be used until definitive treatment (such as lung transplantation for patients with end-stage pulmonary disease), or spontaneous recovery (such as phrenic neuropraxia or axonotmesis following cardiac surgery) can occur.
    (b) Palliative care. In patients in end-stage respiratory failure, for whatever cause, short-term ventilation is an option to be used as a temporizing device to allow the child to be discharged home, allowing (if that is the parents' wishes) to be cared for and die at home rather than in hospital. An example would be extubation to noninvasive ventilation (even if required 24 h/day) to allow for discharge home where the family's wishes are for the child to spend their remaining time at home (Chap. 5).

Who?

Once the rationale for chronic ventilation is accepted, consideration of which patients are most likely to benefit from chronic ventilation then follows. It should be noted, however, that there is actually no consensus on how much of a role the above factors should play in deciding precisely which child should be offered long-term ventilation. Consequently there is marked variability in both modes of ventilation employed and types of patients offered long-term ventilation, as well as in the criteria to use to determine exactly when chronic ventilation should be initiated. In simple terms children requiring long-term ventilation generally fall into five broad disease categories.

The most common cause of chronic hypoventilation is respiratory muscle failure, due either to a primary disorder of respiratory muscle or neuromotor function or failure of normal respiratory muscles in the presence of excess load due to primary pulmonary or thoracic cage disorders.

1. Progressive neuromotor disease (Chap. 14). These disorders are characterized by progressive loss of skeletal muscle function. With involvement of thoracic cage and respiratory motor function, these patients inevitably develop a variety of respiratory sequelae.

   (a) Progressive pulmonary restrictive defect. This commonly arises in association with disturbances in thoracic cage and spinal anatomy (scoliosis), as well as the decreased range of motion of the chest wall, resulting in progressive deterioration in respiratory system compliance and loss of lung volumes [27].
   (b) Increasing risk of opportunistic infections. Due to decrements in respiratory muscle strength, as well as reduced ability to achieve maximal inspiration, these patients have deterioration in cough effectiveness, and hence reduced ability to clear retained secretions, associated with increasing risks of opportunistic infections [23].
   (c) Increasing hypoventilation. Patients with respiratory muscle weakness, particularly if involving diaphragmatic function, may be able to "compensate" (at least initially) by use of accessory muscles of respiration. They may, however, show hypoventilation specifically in REM sleep, due to the relative loss of skeletal motor activity associated with REM-related alpha premotor neuron inhibition. Infants are particularly at risk, due to both the fact that, due to their increased thoracic cage compliance [37], they are more dependent upon diaphragmatic function for normal respiration, but also due to the significantly greater quantity of REM sleep required by infants [38].

   These disorders can be divided into two groups, based on their primary pathophysiology.

   - Diseases primarily affecting respiratory motor neuron function, either specifically to respiratory motor neurons, such as due to phrenic nerve damage from surgery or trauma, or as part of a more generalized disorder of spinal motor neurons, such as spinal muscle atrophy (SMA). SMA is characterized by progressive skeletal muscle weakness consequent to atrophy of spinal alpha motor neurons [39]. It is divided into four categories, based on age of presentation and rapidity of progression, with type 1 having the worst prognosis (death occurring usually, without respiratory support, in the first 2 years of life). In the more severe types, hypoventilation is to be expected, with initiation of respiratory support (primarily noninvasive) resulting in significant improvements in life expectancy [40]. Specifically for type 1 patients, since invasive ventilation does not appear to add to life expectancy (compared to noninvasive) while contributing to the loss of ability to communicate [41], invasive ventilation is generally considered inappropriate as a therapeutic option for this patient population [42, 43].
   - Diseases primarily affecting respiratory muscle function, such as the muscular dystrophies, with Duchenne muscular dystrophy (DMD) comprising the largest population [44].

2. Severe respiratory disease. Compared to adults (e.g., COPD), there are relatively few clinical scenarios where a child can be expected to have chronic, stable hypercapnia secondary to a primary pulmonary disease.

   (a) Cystic fibrosis. Noninvasive ventilation has not been shown to increase the life expectancy of patients with cystic fibrosis, while invasive ventilation (due to the adverse consequences of tracheostomy on the ability to cough and clear secretions) is rarely employed. There is some evidence, admittedly in small numbers, that noninvasive ventilation may help in terms of airway clearance, as well as nocturnal gas exchange and quality of life [45], in patients with severe pulmonary disease [2, 46]. It has also been employed for patients with end-stage cystic fibrosis awaiting lung transplant and has been successful in maintaining reasonably good health until a donor organ becomes available [47]. Given its limited success in patients with cystic fibrosis, invasive ventilation is rarely employed [48].

   (b) Bronchopulmonary dysplasia (BPD). Consequent to the appreciation of the role oxygen and ventilation play in the generation of BPD in general, efforts are now made to limit as much as possible the initiation or maintenance of ventilator support in children born prematurely [49]. Despite these efforts, there remains a small population, however, with chronic, severe lung disease that requires ongoing ventilation for survival. For example, 7 % of children in the Massachusetts population of home-ventilated children had chronic lung disease due to prematurity [4] (Chap. 15).

3. Static or progressive disease affecting thoracic cage.

   (a) Scoliosis. Scoliosis is probably the most common skeletal deformity resulting in respiratory impairment. The lateral curvature of the spine in scoliosis results in compression of the ribs, and thereby the lung, on the concave side, with spreading of the ribs on the convex side, resulting in overstretched muscles, with reduced respiratory muscle efficiency and thoracic cage compliance [50]. The impact of scoliosis on respiratory function is directly affected by both the severity of the scoliosis and whether it is idiopathic, with otherwise normal respiratory muscle function, or developing in the context of a progressive neuromotor disorder, such as DMD [51, 52]. Both the reduced thoracic cage compliance and (if starting early enough in lung development) the associated reduction in lung growth increase the work of breathing, in severe cases sufficient to overload the respiratory muscles, resulting in hypoventilation (initially during REM sleep, but, if severe enough, eventually resulting in daytime hypoventilation). Treatment is primarily surgical, mainly to prevent progression since it rarely is associated with subsequent improvement in lung function [50]. In more severe cases, particularly patients with associated neuromotor disease, ongoing ventilatory support may be required [50].

   (b) Primary chest wall disorders. This comprises a diverse, and generally rare, group of disorders [50], which can include:

- Restrictive defects, such as asphyxiating thoracic dystrophy (Jeune's syndrome) [53]
- Disorders of loss of intrinsic rigidity of the chest wall, such as in traumatic flail chest [50], or following thoracoplasty, historically used for treatment of advanced tuberculosis [50], now rarely employed, and more likely for resection of chest wall malignancies [54]

4. Excess loading of the respiratory system (obstructive sleep apnea, obesity hypoventilation).

   (a) Obstructive sleep apnea (OSA). OSA typically causes nocturnal desaturations associated with significant sleep fragmentation, though usually, except in the more severe cases, without significant or persisting hypoventilation [55]. In more severe cases, or if associated with other disorders (such as Duchenne muscular dystrophy or morbid obesity), the resulting disturbance in respiratory drive may be sufficient to require initiation of ventilatory support (Chap. 13).

   (b) Obesity hypoventilation. With the increasing incidence of obesity (even in children) reported in most societies, there is an increasing incidence of obesity hypoventilation syndrome [56]. Obesity hypoventilation arises as a consequence of a combination of impaired mechanics due to excess respiratory muscle loading and impaired compensatory mechanisms associated with sleep-disordered breathing (many patients also having at least elements of obstructive sleep apnea) [56]. Consequently with increasing obesity, these patients initially develop sleep-related hypoventilation. If respiratory drive is preserved while awake, these patients will be able to maintain daytime normocapnia, explaining why many morbidly obese patients maintain adequate daytime ventilation. A subgroup will, however, develop blunted respiratory drive and consequently daytime hypoventilation. This may be due to individual susceptibility [57], but can occur as a primary hypothalamic disorder, with both hyperphagia and intrinsic blunting of respiratory drive (below) [58].

5. Disorders affecting respiratory drive (central hypoventilation syndromes). Respiratory control can be divided into voluntary (cerebral cortex) and involuntary (brainstem). Normal respiration is dependent upon a complex integration of a rhythmic pattern of respiratory motor activity, generated by the central pattern generator (CPG) within the pons and medulla, with ongoing adaptation to afferent information from the peripheral arterial chemoreceptors (carotid and aortic bodies), central chemoreceptors (brainstem), intrapulmonary receptors, and respiratory muscle mechanoreceptors [59]. The CPG is comprised of a complex network of neuron groups that control and drive respiratory muscle activity, including the upper airway muscles, during discrete phases of the respiratory cycle: pre-inspiration, inspiration, active expiration, and passive expiration [60]. The major CPG neuron groups are the pontine respiratory group, the medullary neuron groups including the pre-Botzinger complex and Botzinger

complex, and the ventral respiratory neuron groups. CPG activity is modulated in part via inputs from neurons in the dorsal medulla (dorsal respiratory group), including the nucleus tractus solitarius (NTS), which relays pulmonary mechanoreceptor, peripheral chemoreceptor, and other visceral afferent sensory inputs [61]. Located in the ventral medulla, neurons in the retrotrapezoid nucleus (RTN) are modulated by CO_2 and receive input from other CO_2-sensitive areas as well as input from the peripheral chemoreceptors. The RTN interacts with pre-Botzinger and Botzinger neurons to modulate CPG activity, and it appears to serve as an important site for integration of CO_2 and O_2 chemosensory drive. Under normal circumstances, this results in a three-phase respiratory pattern: inspiration (abduction of upper airway and diaphragmatic contraction), post-inspiration (adduction of the larynx, thereby increasing airway resistance and hence slowing of expiratory airflow), and stage 2 (late) expiration (with, in normal circumstances, low levels of internal intercostal and abdominal muscle activity) [61]. Feedback from afferent neurons which respond to changes in respiratory system mechanics, such as with cardiorespiratory disease, induces adaptive changes in respiratory patterns [62]. Any disorder that results in impairment of this interaction of internal rhythm generation with adaptation to external stimuli will therefore result in disturbed ventilatory control and hence central hypoventilation.

(a) Primary dysfunction of the respiratory nuclei, such as congenital central hypoventilation syndrome (CCHS) (Chap. 17)

- CCHS arises due to mutations (primarily polyalanine repeat expansions) in the *PHOX2B* gene [63]. Although congenital, CCHS can present at any age, the degree clinical involvement being linked to the number of polyalanine repeats [63]. CCHS is associated with a variety of disorders of autonomic function, as well as increased risk of neural crest tumors [63]. The primary respiratory disorder is alveolar hypoventilation due blunted central respiratory drive [64], necessitating lifelong respiratory support, the degree of involvement determining whether invasive versus noninvasive. Individuals presenting in infancy (the more severely affected) generally require invasive ventilation, though, as with those presenting later in life, with improvements in spontaneous ventilation with age, they may later be weaned to noninvasive ventilation solely during sleep [63].
- Other. A variety of other congenital disorders involving both autonomic and hypothalamic function have been associated with varying degrees of central hypoventilation [58]. Some are static and some rapidly progressive, with ventilatory support necessary depending upon the degree of nocturnal hypoventilation. A number of these syndromes are associated with abnormalities in appetite regulation, with the hyperphagia and resulting obesity increasing the risk of hypoventilation (above).

b. Secondary to trauma to the respiratory nuclei (Chiari malformation, brainstem tumor, spinal cord trauma) or to respiratory motor function (spinal cord trauma, with damage to phrenic nerve nuclei) (Chap. 16)

When?

Although the need for long-term ventilation can arise as a consequence of a sudden, catastrophic illness, most children requiring long-term ventilation suffer from a progressive disease where the development of respiratory failure is an expected and inevitable sequel of their disease. This does, therefore, allow for anticipatory guidance, giving the family, patient, and their medical team time to discuss and plan for the future and thereby have a clear understanding and preparation for what chronic ventilation entails before it becomes a necessary treatment. Eventual hypoventilation is predictable in many patients with progressive neuromuscular or pulmonary disease. The optimal time, and particularly what criteria to be used to determine exactly when ventilator support should be initiated, remains somewhat controversial and almost certainly has to be individualized for each patient [65].

1. Blood gases.
   (a) Arterial/capillary blood gas. Although this is the "gold standard" for measuring ventilatory status, it is invasive, difficult to do while the patient is asleep, and only gives values for one moment in time (though bicarbonate level provides an estimate of chronicity of hypoventilation). It is therefore primarily of use to document awake hypercapnia.
   (b) Pulse oximetry. Pulse oximetry has the attraction that it provides a continuous, noninvasive record that can be obtained during sleep. It is also a surrogate for hypercapnia, since, at a constant inspired oxygen concentration, any rise in arterial carbon dioxide level, as described by the alveolar gas equation, results in a reduction in alveolar oxygen pressure (pAO_2) and hence a proportionate fall in arterial oxygen pressure (paO_2) [66]. Consequently any elevation in arterial carbon dioxide above 50 mmHg pressure (so long as the child is breathing room air) will perforce cause a fall in saturation. There are, however, a number of situations where it can provide erroneous information [67], as well as not providing information on sleep state (i.e., whether SWS or REM sleep was ever achieved).
   (c) Noninvasive carbon dioxide (CO_2) monitoring (transcutaneous or end tidal). Both of these methodologies allow for continuous monitoring of carbon dioxide levels. They both, however, have their limitations in terms of ease of obtaining and reliability of data obtained [68].
   (d) Combination. Allowing for their limitations, combining both CO_2 and O_2 can be used as a home-based tool in evaluating sleep-related hypoventilation

[69, 70], though, again, limited by the absence of any information on sleep state.

2. Clinical. Most patients requiring chronic ventilation suffer from a progressive disease, the hypoventilation arising insidiously as a result of slow deterioration of their clinical status. Consequently these patients may adapt to this deterioration and become tolerant of the resulting impact on their respiratory function and, as a result, be remarkably (at least perceived) asymptomatic [14, 71]. Clinical assessment is therefore notoriously unreliable in this patient population. Despite this, a number of authorities have, however, suggested using clinical assessment to determine both need for, and also adequacy of ventilatory support, primarily in patients with neuromotor disease.

   (a) Symptoms of nocturnal hypoventilation. As noted, because of the REM-associated skeletal hypotonia, sleep-related hypoventilation is most likely to occur, at first, during REM sleep. Associated symptoms include frequent awakenings, night sweats, nightmares, nocturnal enuresis, morning headaches, daytime hypersomnolence, and decreased daytime performance [72].
   (b) Respiratory pattern. The diaphragm is the primary muscle of inspiration in normal individuals at rest, with the external intercostals being adjunct inspiratory muscles and the internal intercostals being expiratory muscles and usually only active during exercise or forced expiration [22]. With respiratory muscle fatigue, there may become evidence of recruitment of accessory muscles of respiration (intercostals and shoulder girdle) even at rest. Moreover, with increasing muscle weakness, paradoxical respiration may become apparent. Normally chest and abdominal compartments move in synchrony during respiration. With intercostal muscle weakness, particularly if the upper airway is also involved, increasing upper airway resistance, then on inspiration the abdomen moves out, but the chest wall moves in. In contrast, with predominantly diaphragmatic weakness, where the accessory muscles become the primary muscles of respiration, the chest wall moves out on inspiration, yet the abdomen is sucked in. Consequently evaluation of the patient's respiratory pattern can provide a significant amount of information regarding their respiratory reserve and muscle groups involved [22].

3. Polysomnography. Nocturnal polysomnography (where available) is the "gold standard" for diagnosing sleep-related breathing disorders and in particular nocturnal hypoventilation not associated with daytime hypoventilation [23, 42]. It is really the only methodology to ensure that all sleep stages were in fact seen, since patients who never get below light (stage 2) sleep may have very different ventilation patterns compared to patients with long period of REM or slow wave sleep [18] (above). It is also the only methodology of quantifying the impact therapeutic maneuvers (e.g., nocturnal ventilation) have on sleep architecture. Since pulse oximetry and continuous CO_2 monitoring are also integral components, polysomnography therefore provides a continuous evaluation of respiratory status, not only in response to changing sleep state but also to therapeutic maneuvers. Polysomnography is, however, labor intensive (and hence relatively

expensive) and, in many centers, of limited availability. Moreover, given the complexity of sensors employed, and the adverse impact the sleep laboratory environment may have on sleep, as well as the fact that only 1, perhaps 2, nights can be studied, some authorities have questioned whether polysomnography is either reliable or necessary and recommended using symptoms, supported by oximetry and carbon dioxide monitoring instead to assess adequacy of nocturnal ventilation [73].

4. Pulmonary function. Pulmonary function testing is a readily available, noninvasive, standardized method of measuring both progression of respiratory status and respiratory muscle function. It can be performed by most cognitively intact children aged 6 years and over. It therefore holds attraction as a potential method (especially in patients with slowly progressive neuromotor or pulmonary disease) for predicting the necessity for initiation of ventilation.

   (a) Pulmonary disease. Most of the data linking pulmonary function to respiratory status comes from patients with cystic fibrosis (CF), the severity of which, as a primarily airways disease, is best assessed using the forced expiratory volume in 1 s (FEV_1). As a general rule, the probability of survival of greater than 2 years of patients whose FEV_1 is less than 30 % predicted is under 50 % [74]. This is a relatively old data, but gives a value at which hypercapnic respiratory failure (either due to progression of the disease or, as is commonly seen, acute deterioration associated with an additional viral infection) becomes increasingly likely. Although influenced by many factors (age, nutritional status, rapidity of progression, opportunistic infection) in patients with progressive pulmonary disease, formal evaluation of nocturnal ventilatory status (oximetry or polysomnography) should be considered once their FEV_1 falls below 40 % predicted [75].

   (b) Neuromotor disease. Most of the data linking pulmonary function to respiratory status comes from patients with DMD, as a disease where patients are cognitively intact, and survival expected well past the age where the patients can perform reliable pulmonary function testing. Since these disorders cause primarily a restrictive pulmonary defect, the inspiratory vital capacity (IVC) provides the most reliable predictor of nocturnal hypoventilation, with increasing risk once IVC falls below 40 % predicted [14, 65, 76], though an FEV_1 of less than 40 % has also been suggested as a useful predictor of sleep-related hypoventilation [77]. Alternatively, at least in adults, peak cough flow has been shown to be a useful indicator, with flows of less than 160 L per minute being predictors for the need for assisted ventilation [65, 78]. Appropriate values for children have not, however, been established. Part of the problem with the above tests is that they require maintenance of an oral seal to perform the test, which can be difficult in individuals with neuromotor disease. Since this is not required for sniff nasal inspiratory pressure (SNIP), this may offer a useful alternative [79], though again values predictive of the need for ventilation, particularly in children, have yet to be determined.

Conclusion

Long-term ventilation, primarily with the aim for discharge to home, has become a routine therapeutic option for children with nocturnal or persisting hypoventilation. Even though it has now essentially become a standard of care for many clinical situations, there still remains debate about the precise indications (which patients are most likely to benefit), the criteria for its initiation, and what is the optimal methodology to use in individual patients. Despite these limitations, clinical experience, born out by patient and parental reports, is that for many children, it has resulted in dramatic improvements in not only longevity but also quality of life, allowing safe discharge to home for many children who previously faced spending the remainder of their life in hospital. With its apparent effectiveness, it is difficult to ethically justify randomized controlled trials. Despite this, with its resulting increasing use, and resulting longitudinal evaluation of larger populations, we will hopefully be better placed to answer exactly which patients would most benefit and the optimal timing for its initiation.

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