Journal of Neuromuscular Diseases 10 (2023) 1075–1082
DOI 10.3233/JND-230053
IOS Press

Research Report

Respiratory Insufficiency in Neuromuscular Disease (RIND): A Delphi Study to Establish Consensus Criteria to Define and Diagnose Hypoventilation in Pediatric Neuromuscular Disease

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Accepted 29 September 2023
Pre-press 25 October 2023
Published 7 November 2023

Abstract. Chronic respiratory failure is a common endpoint in the loss of respiratory muscle function in patients with progressive neuromuscular disease (NMD). Identifying the onset of hypoventilation is critical to allow for the timely introduction of ventilator support and effectively manage respiratory failure [1–3]. While there are accepted criteria governing the diagnosis of hypoventilation during polysomnography (PSG) [4], there is concern that criteria are insufficient for identifying hypoventilation in the earlier stages of respiratory insufficiency related to NMD. The purpose of this project was to identify more sensitive criteria for identifying hypoventilation.

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ISSN 2214-3599

Methods: Fifteen pediatric pulmonologists with broad experience in managing patients with NMD, 10 of whom were board certified in and practice sleep medicine, were assembled and performed a review of the pertinent literature and a two-round Delphi process with 6 domains (Table 1).
Results: Within the 6 domains there were three pertinent items per domain (Table 2). There was clear agreement on findings on history (morning headaches) and pulmonary function testing (FVC < 50% or awake TcCO2 > 45 mmHg) indicating a high concern for nocturnal hypoventilation. There was close agreement on the definitions for nocturnal hypercapnia and hypoxemia. PSG criteria were identified that indicate a patient is likely in the transitional phase from adequate ventilation to hypoventilation.
Discussion: We identified a set of clinical criteria that may allow for more sensitive diagnosis of hypoventilation in NMD and earlier initiation of non-invasive ventilation leading to a reduction in the respiratory morbidity in progressive NMD. These criteria need to be further and more broadly validated prospectively to confirm their utility.

Keywords: Neuromuscular, Respiratory failure,hypoventilation, polysomnography, capnography

INTRODUCTION

Chronic respiratory failure is the most common cause of morbidity and mortality for individuals with neuromuscular disease (NMD). While the onset of respiratory failure in the acute setting is well-defined, the onset of chronic respiratory failure is often insidious and its evolution is poorly recognized and described. Presenting first as nocturnal hypoventilation, identifying this change is subtle clinically and often depends on the patient's and family's reporting of symptoms and the clinician having a high level of concern and suspicion. However, in younger patients or those with intellectual disabilities, it may be hard for patients to convey symptoms and for caregivers to recognize them.

Non-invasive ventilation (NIV) is used to treat sleep disordered breathing and chronic respiratory failure and has been previously shown to improve survival, quality of life and well-being [1, 3]. Therefore, early recognition of hypoventilation and initiation of NIV for sleep disordered breathing and chronic respiratory failure is paramount for individuals with NMD.

Polysomnography (PSG) is the gold standard test to evaluate for sleep disordered breathing, and in particular nocturnal hypoventilation. However, access to PSG is often limited. Furthermore, PSG may be performed without capnography in some centers making it impossible to accurately identify early hypercapnic respiratory failure before it gets more established and/or progresses to daytime hypercapnea. This presents a challenge, on top of the limited access to PSG, in that implementation of clinical guideline recommendations of surveillance PSG at the time of diagnosis of a NMD [5] or after a patient reaches a certain clinical state is not practical. There have been a wide range of approaches to assessment and management of hypoventilation in pediatric patients with neuromuscular disease; [6–9] however, more recent guidelines have shifted towards taking a more proactive approach, focusing on awareness of when a patient is at risk for hypoventilation and when it is important to obtain a PSG in order to maximize diagnostic yield [10–16] so that early therapeutic intervention can occur.

The only reliable way to identify nocturnal hypoventilation is by using transcutaneous or end-tidal capnometry during the PSG. The absence of this important data can lead to under-reporting of nocturnal hypoventilation. By themselves, nocturnal pulse oximetry and daytime carbon dioxide (CO_2) by venous or arterial blood gas are insensitive in detecting nocturnal hypoventilation [2]. In addition, the broad category of "sleep disordered breathing", including both obstructive sleep apnea and hypoventilation, does not offer the specificity needed to accurately diagnose the true respiratory status, which may have features of both obstructive physiology and hypoventilation [17, 18].

An additional challenge is the varying definition of nocturnal hypoventilation. The American Academy of Sleep Medicine (AASM) has different pediatric and adult diagnostic criteria with an option to use either criterion for children between 13–18 years of age. Furthermore, in 2018, specific recommendations were published for the prescription of NIV for individuals with Duchenne muscular dystrophy and spinal muscular atrophy, based on expert opinion [4, 13, 19]. Because of the desire to identify and treat hypoventilation early, these guidelines recommended much less stringent criteria for the diagnosis of nocturnal hypoventilation as compared to the AASM criteria. This is not to suggest that the AASM criteria are wrong per se, but that patients with neuromuscular disease have different respiratory physiology

and consequences of transitioning from normal ventilation into hypoventilation than otherwise healthy patients. Daytime hypoventilation is a late finding in the evolution of respiratory insufficiency in NMD, with respiratory consequences clearly established. Accurate detection of nocturnal hypoventilation in the absence of daytime hypercapnia has a pathophysiological rationale, since nocturnal hypoventilation precedes the development of overt respiratory failure in NMD patients [20, 21]. As such it is important to consider an alternate set of criteria for identifying sleep-related respiratory insufficiency earlier in patients with neuromuscular disease.

There are a number of specific challenges associated with using the existing criteria.

First, hypoventilation needs to be defined in the context of neuromuscular disease and it needs to be acknowledged that it is not a respiratory condition that is present only during sleep, like obstructive sleep apnea (OSA), but instead can extend into wakefulness. Second, while listing the parameters to be reported on PSG, the American Academy of Sleep Medicine (AASM) Scoring Manual [22] places the priority of reporting hypoventilation in adults as "Optional", and as "Recommended" for children. This does not allow for consistency in testing, and hence, a perceived lack of need for capnometry in adult PSG studies. Third, the current AASM guidelines define alveolar hypoventilation in the context of OSA where obstructive apneas and hypopneas predominate. However, in NMD, hypoventilation can present with non-obstructive hypopnea in the absence of or with a paucity of obstructive apnea. Finally, as nocturnal hypoventilation in NMD portends progression to diurnal respiratory failure, it should be classified as a diagnosis distinct from other forms of sleep disordered breathing (obstructive and central sleep apneas, etc.). Therefore, clinical and polysomnographic criteria for the detection of NMD-related respiratory insufficiency and/or related hypoventilation should be considered distinct and unique from the standard AASM criteria. The overarching aim of this study was to develop consensus criteria for the diagnosis of hypoventilation in individuals with NMD.

METHODS

We conducted a Delphi process comprising comprehensive item generation followed by consensus building by an international expert panel to identify items of critical importance. The process was conducted between August 2019 and February 2020.

Participants

The lead investigator (OHM) engaged a sample of international pediatric pulmonologists and sleep physicians with expertise in pediatric NMD to participate in the Delphi process.

Item generation

Items were generated from two sources. The lead investigator (OHM) performed a scoping review to identify guidelines for the definition of hypoventilation and sleep disordered breathing in patients with neuromuscular disease. A systematic search of the published literature was conducted from 1969 to 2019. Electronic databases which were searched included the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, CINAHL, EMBASE, LILACS and Web of Science. The literature results were then summarized and presented to the expert committee. The expert committee met in person during the 2019 American Thoracic Conference to review the results of the literature review and to discuss current clinical practice. The expert panel also added manuscripts to results of the literature review to move forward for the Delphi process.

Delphi consensus methods

We performed a two round Delphi process. In Round 1, a total of 6 open-ended questions were posed to the group including questions relating to history and physical examination, pulmonary function testing, polysomnograms, as well as criteria for defining hypercapnia and hypoxemia in this patient population (Table 1). Additional items for each question could be added by the participants.

In Round 1, for questions 1, 2, 5, and 6, the participants were asked to answer the questions based on their own experience, and for questions 3 and 4, based on established criteria for hypoxemia and hypoventilation. The participants were then asked to rank the answers or add in their own sense of the clinical utility of each criterion. The Round 1 results were culled, with similar written-in answers batched together, and then rated based on how frequently they were mentioned and all answers that were mentioned by at least 20% of the 15 respondents were used in Round 2. Prior to the Round 2 rankings the group reviewed the culled results and approved unan-

Table 1
Round 1 Questions that were included as part of the Delphi Study

Questions
1. What components of a history and physical makes you concerned about hypoventilation/RIND and would prompt you to get capnography/PSG?
2. Are there other objective data that make you concerned about the possibility of hypoventilation/RIND?
3. Which criteria do you feel most specifically or best identifies clinically significant hypercarbia on capnography/PSG?
4. Which criteria do you feel most specifically or best identifies clinically significant hypoxemia on PSG?
5. What non-gas exchange parameters on a PSG help to define RIND?
6. How would you define the pre-respiratory failure/transition stage on PSG?

imously the ranking questions that were the Round 2 questions. From the Round 2 results the criteria that had the highest support among the committee members were identified and were organized into the formal recommendations.

The results were reported as the mean of the 15 ratings per question. The rating of the questions was by preference with "1" representing the highest score with subsequent increasing ordinal numbers representing lower scores. Table 1 lists the questions and number of choices associated with each question. The answer choices that were in the top half of the ratings per question were defined as the majority opinion.

RESULTS

Fifteen pediatric pulmonologists with expertise in the pulmonary management neuromuscular disease, of whom 10 practice sleep medicine participated in the Delphi process. These 15 participants represented 13 different hospitals across 5 countries (United States 9, Canada 3, Australia 1, England 1, and France 1). The participation rate was 100% with all 15 participants completing both Rounds 1 and 2.

The scoping review resulted in the identification of 4 relevant clinical practice guidelines [13, 18, 19, 22]. After the in-person meeting with the expert panel, from these clinical practice guidelines, the identified items were summarized into 6 domains with one question per domain as follows: 1) history and physical examination findings suggestive of hypoventilation; 2) pulmonary function findings suggestive of hypoventilation; 3) definition of hypoxemia; 4) definition of hypercapnia; 5) polysomnography findings; 6) findings suggestive of pre-hypoventilation.

Table 2

Question 1: What components of a history and physical makes you concerned about hypoventilation/RIND and would prompt you to get capnography/PSG?
1. Morning headaches
2. Poor sleep quality
3. Daytime somnolence
4. Increased fatigue

Question 2: Are there other objective data that make you concerned about the possibility of hypoventilation/RIND?
1. FVC < 50% predicted
2. TcCO2 > 45 mm Hg during the day
3. Awake SpO2 < 95%

Question 3: Which criteria do you feel most specifically or best identifies clinically significant hypercarbia on capnography/PSG in NMD?
1. TcCO2 > 45 mmHg for 25% sleep
2. TcCO2 > 50 mmHg for > 2% sleep or 5 min continuously
3. TcCO2 increase 10 mmHg above baseline for 2% of sleep

Question 4: Which criteria do you feel most specifically or best identifies clinically significant hypoxemia on PSG?
1. Mean SpO2 < 94%
2. SpO2 < 90% for > 2% sleep
3. SpO2 < 90% for > 5 min continuously

Question 5: What non-gas exchange parameters on a PSG help to define RIND?
1. Increased hypopnea, including those scored as central events
2. Tachypnea relative to age
3. Increased RR in REM relative to NREM

Question 6: How would you define the pre-respiratory failure/transition stage on PSG?
1. Apnea hypopnea index > 5/hr
2. Tachypnea > 25% above baseline from sleep onset
3. Paradoxical breathing and increased WOB and normal gas exchange

For Round 1, Questions 1, 2, 5, and 6 were open ended. Questions 3 and 4 had 4 and 3 items, respectively. Questions 3 and 4 were answered in Round 1 with a total of 6 items (Table 2).

For Round 2 there were 4 domains and a total of 28 items. At the end of Round 2, there were 4 domains and a total of 12 items. See Table 2 for the final list of 6 domains and 18 items that achieved consensus.

At the follow-up meeting with the expert panel to discuss the results, a new paradigm called Respiratory Insufficiency in Neuromuscular Disease (RIND) was defined and included the different stages of progressive respiratory insufficiency as well as the diagnostic criteria.

There were several key recommendations from the group's consensus:

1. There was clear agreement on findings on history (morning headaches) and pulmonary function testing (FVC < 50% or awake TcCO2 > 45 mmHg) indicating a high concern for nocturnal hypoventilation and a need to get confirmatory testing by PSG.
2. There was close agreement on the definitions for nocturnal hypercapnia and hypoxemia.
3. There were identified criteria from the PSG that indicated a patient is 'at risk' and in the transitional phase from adequate ventilation to hypoventilation.

DISCUSSION

We are describing for the first time a new paradigm called Respiratory Insufficiency in Neuromuscular Disease (RIND). RIND considers the unique respiratory considerations of the neuromuscular disease population through a description of the different stages of progressive respiratory insufficiency as well as defining unique diagnostic criteria. A patient with progressive neuromuscular weakness transitions through a continuum of four broad stages: i) normal ventilation; ii) at risk for hypoventilation during physiological stresses such as acute illness, surgery, etc.; iii) nocturnal alveolar ventilation; and iv) nocturnal and diurnal alveolar hypoventilation (continuous respiratory failure).

The current definitions of sleep-related alveolar hypoventilation do not take into consideration the uniqueness of patients with NMD. These patients have a progressive reduction in respiratory system compliance due to loss of lung volume and restrictive thoracic dystrophy [23–25]. These patients slowly and inexorably progress towards respiratory failure as opposed to having a more acute deterioration. This transitional phase is extremely important to recognize and follow to implement proactive management and maintain close follow-up and assessment in order to minimize respiratory morbidity. This graded approach to hypoventilation, as opposed to defining it as present or not-present, also has the potential allow for better classification of risk of impending respiratory morbidity.

The transition often involves a rapid, shallow breathing pattern and increasing thoracoabdominal asynchrony. The rapid, shallow breathing is an adaptive mechanism using lower tidal volume and expansion of a poorly compliant respiratory system, and a higher respiratory rate, which increases metabolic demand [26]. In the longer term, rapid shallow breathing leads to progressive atelectasis due to reduced tidal expansion of the lungs. With further worsening of lung compliance, additional decrease in tidal volume can increase dead-space ventilation, and eventually produce hypercapnea. In addition, patients may linger in states of borderline, impending or pre-respiratory failure before experiencing a stressful event (illness, surgery, etc.) that precipitates overt respiratory failure.

In considering PSG identification of these stages, it is exceptionally important to recognize that the interpretation of the PSG needs to be done in the context of the underlying NMD. This group of experts agreed that hypoventilation will be missed if accurate capnometry is not measured during a PSG or if a patient with NMD experiences frequent nocturnal arousals (spontaneous or respiratory event related) and/or tachypnea preventing the recording of an accurate continuous CO_2 levels overnight. The challenge to this lies in describing the likely clinical signs/symptoms and PSG features that should raise concerns for potential or impending respiratory insufficiency and prompt the treating clinician to be ready to initiate non-invasive ventilation during an acute illness.

Previous studies have shown that a $PaCO_2$ of > 45 mm Hg while awake was a sensitive (91%) and specific (75%) indicator of respiratory insufficiency, while a base excess of > 4 mmol/L was highly specific (100%) but less sensitive (55%) [27]. However, it could be argued that many such studies were conducted when respiratory insufficiency of NMD was already well established and pulmonary restriction was at least moderate to severe. In a study on adults with a variety of NMD managed by invasive and non-invasive ventilation, *Bauman, et. al.* demonstrated that normal daytime capnometry, oxygen desaturation, body mass index, and forced vital capacity (FVC) were poor predictors of nocturnal hypoventilation [28]. Furthermore FVC% and PEF% measurements may not be feasible in patients under 6 years of age, which limits its utility as a longitudinal predictive measure in younger patients at risk for hypoventilation; unfortunately, there is not a reasonable surrogate measurement. In a separate study of children with NMD, pulmonary function correlated poorly with nocturnal hypoxemia and hypercapnia and normal daytime gas exchange [18]. *Paiva et al.* showed nocturnal pulse oximetry and daytime arterial

blood gases to be insensitive in diagnosing nocturnal hypercapnia in children with NMD who are managed with non-invasive ventilation [2].

The AASM threshold for nocturnal hypoventilation is an $EtCO_2/TcCO_2 > 50$ mmHg for 25% of sleep time [22]. However, alternate definitions have been proposed that identify hypoventilation in patients with NMD as occurring earlier in progression of respiratory disease [4]. Considering these, the proposed criteria for hypoventilation, in order of preference, are: $TcCO_2 > 45$ mm Hg for > 25% of sleep, $TcCO_2 > 50$ mm Hg for > 2% sleep or 5 minutes continuously, and $TcCO_2$ increase 10 mmHg above baseline for > 2% sleep. In addition, the criteria for hypoxemic respiratory failure were: mean $SpO_2 < 94\%$, $SpO_2 < 90\%$ for > 2% sleep, and $SpO_2 < 90\%$ for > 5 minutes continuously.

The advantage of these new criteria is that they acknowledge that respiratory insufficiency can present in a variety of ways, all of which are important and need to be considered. These include: a mild, but prolonged deficiency in gas exchange ($TcCO_2 > 45$ mm Hg for > 25% of sleep or a mean $SpO_2 < 94\%$); a more severe gas exchange deficiency for a short period of time ($TcCO_2 > 50$ mm Hg for > 2% sleep or 5 minutes continuously and $SpO_2 < 90$ for > 2% sleep or 5 minutes continuously); and a significant change in baseline gas exchange ($TcCO_2$ increase 10 mmHg above baseline for > 2% sleep) following sleep onset. These criteria are not meant to indicate severity, but simply that patients can present with respiratory insufficiency in a variety of ways, all of which are important to recognize.

As is done with other pulmonary function measures, such as FVC%, peak expiratory flow % predicted (PEF%), SpO_2, and $PaCO_2$, normal needs to be put into perspective. Patients can remain eucapnic with tachypnea to maintain optimal minute ventilation in sleep. The group remains concerned that these "at risk" categories of patients are not often identified by pulmonary function or other daytime metrics and patients in this transitional phase may not be identified until they suffer acute respiratory failure during an acute illness. A $PaCO_2$ of 44 mm Hg in a patient who can speak in full sentences, is not using accessory respiratory muscles and has a normal respiratory rate is appropriately called "normal". However, that same $PaCO_2$ of 44 mm Hg in a child who is dyspneic, with intercostal and subcostal retractions or thoracoabdominal asynchrony and tachypnea would still be in normal range but would not be "normal" for that patient considering the adaptations that that patient has made to breathe. While this concept is often made clear during early clinical training in managing a patient in status asthmaticus, the same concept for a patient with neuromuscular disease who is at risk of chronic respiratory failure has neither been acknowledged nor made clear. The group addressed this in Questions 5 and 6 and while there was some overlap between the signs proposed, there were two clear themes: increased work of breathing or thoracoabdominal asynchrony with tachypnea.

It common for patients with NMD to have some amount of thoracoabdominal asynchrony (TAA) due to abnormal respiratory compliance and the need for greater diaphragm contraction producing greater outward abdominal motion to overcome it. It was felt that this, partnered with additional nocturnal respiratory abnormalities such as oxyhemoglobin desaturation and decreased depth of breathing (hypopnea), is an indication of relative hypoventilation (even without overt hypercapnia) or related respiratory weakness, as opposed to obstructive sleep apnea, as it often is often interpreted. The group felt that if the AHI was above 5 or if there was thoracoabdominal asynchrony with tachypnea, that it was a clear indication of respiratory compensation for abnormal mechanics and or respiratory muscle insufficiency. Furthermore, this condition indicates that the patient is at risk for developing respiratory failure with further loss of respiratory muscle strength, but also with an acute catabolic physiologic stress such as an acute illness or recovery from a significant surgery or anesthesia exposure. For these reasons, a patient with these signs would need to be followed closely and with the potential need to initiate ventilation promptly during an acute illness. Separate from TAA, tachypnea is a normal compensation for restrictive respiratory physiology as part of the rapid shallow breathing pattern where lower tidal volume breathing is less energy intensive. The group felt that a 25% increase in respiratory rate above baseline during sleep with preserved gas exchange indicates that the patient is compensating at a high enough level that any further stress could not be managed by the respiratory system and would thus precipitate hypercapneic respiratory failure.

Considerations for clinical evaluation

Once the decision is made to evaluate for hypoventilation the standard approach has been to perform a standard 16-channel polysomnogram. Irrespective of the approach to interpreting the data, this certainly gives the most and likely the highest quality data since

it is performed in a highly controlled and continuously monitored medical environment. This includes information not only on SpO_2 and $EtCO_2$ or $TcCO_2$, but also sleep stage, vital signs, and breathing pattern. The challenges associated with PSGs are the extensive amount of equipment that is attached to the patient and the need for the patient to sleep out of their home environment in a hospital bed with an associated significant departure from their usual care routine. This is especially challenging given the loss of mobility and increased medical fragility of a large proportion of the NMD population.

For these reasons, the alternative approach of just focusing on gas exchange, SpO_2 and $EtCO_2$ or $TcCO_2$ has been used. While still requiring some monitoring and lead attachment, they are nowhere near as onerous (2 channels vs 16). There is also the additional benefit of the patient sleeping in his/her own home environment. However, a challenge of ambulatory oximetry and/or capnography, is in a non-monitored environment there is a potential for lower quality data given the lack of direct observation by a sleep technologist [29]. Recognizing that maintaining an $EtCO_2$ nasal cannula in situ is very difficult, there has been success in using a $TcCO_2$ monitor to reliably evaluate capnography remotely and then transmit the data for review by the patient's treating clinician [30, 31].

CONCLUSION

With the advances across the neuromuscular therapeutics field improving disease management and attenuating the rate of decline and/or improving survival, clinical management of respiratory complications of NMD remains critical. We are reporting a consensus opinion on how to most precisely identify patients with NMD who have significant hypoventilation and/or who are at risk for hypoventilation (transitional hypoventilation) within the framework of respiratory insufficiency in neuromuscular disease. While the findings presented here can improve identification of hypoventilation in patients with neuromuscular disease, further validation of these findings and specific assessment within in sub-types of NMD, such as hypertonic NMD, and in adult patient populations, are needed.

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