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Ambulatory Transcutaneous Carbon Dioxide Monitoring for Children with Neuromuscular Disease

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Dr Shi collected data, carried out the data analysis, drafted the initial manuscript, completed the analysis and interpretation of the data and reviewed and revised the manuscript.

Dr Chiang, Dr McAdam, Dr Goldstein, and Dr Rose all provided substantial contribution to the conception and design of the study as well as the interpretation of the data and critically reviewed and revised the manuscript.

Dr Ambreen, Ms Snow and Ms Mocanu were involved in acquisition of the data and critically reviewed and revised the manuscript.

Dr Amin conceptualized and designed the study, supervised the data analysis and interpretation of the data and critically reviewed and revised all drafts of the manuscript.

All authors drafted/revised the article for intellectual content and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objective: Early screening and diagnosis of nocturnal hypoventilation can slow progression to diurnal hypercapnia and mortality in children with neuromuscular disease (NMD). However, gold standard, laboratory-based polysomnography (PSG) testing is a limited resource. Therefore, we evaluated the diagnostic accuracy of ambulatory transcutaneous carbon dioxide ($tcCO_2$) monitoring used in the home compared to PSG in children with NMD.

Methods: Prospective, cross-sectional study in children 0-18 years old with a confirmed diagnosis of NMD and a clinically indicated need for PSG. Ambulatory $tcCO_2$ was assessed by a respiratory therapist in participant's homes. Demographics, and PSG (including $tcCO_2$).

Results: We enrolled 39 children with NMD; 3 had unusable ambulatory $tcCO_2$ data because of failure of drift correction on the machine (n=2) or an air bubble (n=1). The remaining 36 patients aged 11 months to 16 years (median (IQR) 12.5 years (6.0-15.8)) had ambulatory $tcCO_2$ and outpatient level 1 PSG data. Ambulatory $tcCO_2$ monitoring had a sensitivity of 20.0% (95% confidence interval [CI] 0.5-71.6%) and a specificity of 93.5% (95% CI 78.6-99.2%). Almost all children and/or parents (34/36, 94%) preferred ambulatory monitoring over in-hospital PSG.

Conclusions: Ambulatory transcutaneous carbon dioxide monitoring was not sufficiently accurate as a clinical tool for the diagnosis of nocturnal hypoventilation our cohort of children with neuromuscular disease despite being preferred over PSG by both children and parents.

Keywords: Pediatrics; diagnostic screening programs; hypoventilation; sleep apnea syndromes; neuromuscular diseases; polysomnography.

Abbreviations: sleep-disordered breathing (SDB), neuromuscular disease (NMD), polysomnography (PSG), transcutaneous carbon dioxide (tcCO2), end-tidal carbon dioxide (tcCO2), partial pressure CO_2 (pCO_2), non-invasive ventilation (NIV), continuous positive airway pressure (CPAP), forced vital capacity (FVC), body mass index (BMI), respiratory therapist (RT), American Academy of Sleep Medicine (AASM), electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), oxygen saturation (SaO_2), capillary blood gas (CBG), Duchenne Muscular Dystrophy (DMD), interquartile range (IQR), receiver operating curve (ROC), area under the curve (AUC), confidence interval (CI), standard error (SE), research ethics board (REB)

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1. INTRODUCTION

Early recognition and management of sleep-disordered breathing (SDB), particularly nocturnal hypoventilation, is paramount in reducing mortality in individuals with NMD[1]. The current "gold standard" for diagnosis of nocturnal hypoventilation is a laboratory-based, technician-attended PSG[2]. However, there are currently insufficient resources for the evaluation of sleep-disordered breathing (SDB) in children with neuromuscular diseases (NMD) due to limited and varying resources worldwide[1]. In Canada, it is estimated that 7.5 times more children require polysomnography (PSG) than the current capacity of the healthcare system[3]. The disparity between demand and availability of resources is especially pronounced for children with NMD, as SDB prevalence in this population is estimated to be over 10 times that of the general population, with up to 40% of children with NMD having SDB[4,5].

SDB is defined as the presence of (1) nocturnal hypoventilation, (2) obstructive sleep apnea and/or (3) central sleep apnea. In children with NMD, nocturnal hypoventilation results from insufficient minute ventilation during sleep secondary to respiratory muscle weakness, scoliosis, or obesity from immobility and/or steroid use[6]. Obstructive sleep apnea can result from increased upper airway collapsibility exacerbated by obesity, retrognathia, or macroglossia[6]. Central sleep apnea occurs when intercostal and diaphragm muscle weakness leads to reduced tidal volumes with associated oxygen desaturations during REM sleep. Central sleep apnea also occurs when overall respiratory instability due to obstructive events or sleep-wake transitions leads to further pauses in respiratory effort[6]. Progressive diurnal respiratory insufficiency is preceded by nocturnal hypoventilation. Timely treatment with non-invasive ventilation (NIV) can reduce hospital admissions and prolong survival[1,7].

While there is no consensus on screening frequency, British and American Thoracic Societies recommend at least annual PSGs in non-ambulatory children with NMD, and earlier and/or more frequent studies if SDB symptoms are present[8,9]. Objective testing is necessary because children with NMD and nocturnal hypoventilation are often asymptomatic[10]. Furthermore, child and family centered barriers make PSGs more difficult to complete in children with NMD. These barriers include lack of wheelchair accessibility in the PSG labs; need for safe transfer systems, specialized hospital beds, custom commodes, and frequent patient turning; and significant caregiver burden.

Overnight ambulatory transcutaneous carbon dioxide ($tcCO_2$) monitoring may be an ideal diagnostic tool because it is noninvasive, comfortable, cost-effective, and portable. To date, only two pediatric studies have evaluated overnight home $tcCO_2$ monitoring. Felemban and colleagues demonstrated that ambulatory $tcCO_2$ monitoring was feasible in children with and without NMD who were prescribed NIV[11]. Similarly, Griffon and colleagues showed that ambulatory $tcCO_2$ monitoring was feasible in children on long term ventilation[12]. However, neither study evaluated diagnostic accuracy. Therefore, our study aimed to evaluate the diagnostic accuracy of ambulatory $tcCO_2$, to detect nocturnal hypoventilation in children with NMD compared to the gold standard PSG.

2. METHODS

2.1. Study Design and setting

We conducted a prospective, cross-sectional study between October 1, 2018, and December 31, 2020 at the Hospital for Sick Children in Toronto, Ontario, Canada.

2.2. Participants

Children aged 0 to 18 years old were recruited from the Long-term Ventilation clinic. Inclusion criteria were confirmed NMD diagnosis, clinically indicated PSG as per international societal guidelines[8], and living within a 100 km radius of the hospital. Clinical indications for PSG include signs and symptoms of SDB (eg. snoring, witnessed apneas) and/or being at risk of developing SDB (eg. loss of ambulation, forced vital capacity <60% predicted)[8]. Although children with different NMD diagnoses have variable clinical trajectories, we chose to be inclusive of all diagnoses as the criteria for hypoventilation is the same from age 0-18 years. Also PSG and $tcCO_2$ monitoring can be done in children of all ages[13]. Exclusion criteria were previously known diagnosis of nocturnal hypoventilation, already commenced on long-term invasive and NIV at home, and physician diagnosis of acute upper respiratory tract infection.

2.3. Study Procedures

We collected the following demographic and clinical characteristics from the medical record: age, sex, height, weight, body mass index (BMI) percentile, primary diagnosis, comorbidities, and spirometry (forced vital capacity (FVC)).

Ambulatory Transcutaneous Carbon Dioxide Monitoring

Ambulatory $tcCO_2$ monitoring was performed in the home using the SenTec Digital Monitor carbon dioxide sensor (Therwil, Switzerland). This fully digital sensor is an electrochemical Severinghaus-type CO_2 tension sensor providing continuous CO_2 recordings. Ambulatory data was collected by a respiratory therapist (RT) who traveled to the participant's home to calibrate

and apply the monitor for one night. Calibration is necessary as all sensor measurements drift over time, so an automated correction factor algorithm is applied after the data collection is complete. Our minimum criterion for acceptable recordings was at least 4 hours of data. For each overnight recording, we documented duration of recording; mean, minimum and maximum $tcCO_2$; and time and percentage of the night with a $tcCO_2$ >50 mmHg.

Polysomnography

All PSGs were conducted according to the American Academy of Sleep Medicine (AASM) guidelines with a computer based software system (XL-TEK, Oakville, Ontario, Canada)[13]. A standard overnight PSG includes a 6-lead electroencephalogram (EEG) (C3, C4, O1, O2, M1, M2), two bilateral electro-oculogram (EOG) leads, one submental and two tibial electromyograms (EMG). Respiratory measurements include chest wall and abdominal movement using inductance pneumography; airflow using a nasal cannula connected to a nasal pressure transducer (Braebon); oxygen saturation (SpO_2) using a pulse oximeter (Masimo Irvine, CA); $tcCO_2$ using a Digital Monitor CO_2 sensor (SenTec, Therwil, Switzerland); and end-tidal CO_2 ($etCO_2$) using a Capnocheck (Smiths Medical, Ashford, Kent, UK). PSG video and audio recordings and body position were obtained as per current clinical standards. PSGs were performed and scored by trained sleep technologists independent of the study team. PSGs were then reported by the principal investigator (RA), who remained blinded to the $tcCO_2$ data. We aimed for participants to be booked for a PSG 7-14 days following $tcCO_2$ monitoring.

For our primary study objective, nocturnal hypoventilation was defined by a partial pressure CO_2 (pCO_2) >50mmHg for ≥ 25% of the night, as per the pediatric AASM guidelines, which represents the current threshold used for initiation of ventilation. We additionally analyzed

diagnostic accuracy using a more conservative threshold of pCO_2 >50mmHg for ≥ 2% of the night, as recommended by the 2018 Duchenne Muscular Dystrophy (DMD) Care Considerations Working Group for initiation of assisted ventilation[14]. This definition may be appropriate for diagnosis of nocturnal hypoventilation in other NMD conditions as well.

Patient Experience

We collected subjective data on participant comfort level during the ambulatory home $tcCO_2$ monitoring. Participants (or their parent) were asked to rate their comfort level on a Likert scale with 0 being very uncomfortable and 10 being very comfortable. They were also asked their perception as to the preferred option for diagnostic assessment (i.e., home or in-hospital).

2.4. Study Outcomes

The primary study outcome was accuracy of ambulatory home $tcCO_2$ monitoring for diagnosing nocturnal hypoventilation compared to the gold standard $etCO_2$ during PSG. A secondary outcome was diagnostic accuracy of ambulatory $tcCO_2$ compared to PSG $tcCO_2$ monitoring. Additionally, we evaluated the correlations and agreements between ambulatory $tcCO_2$ and PSG $tcCO_2$ data, comfort level, and diagnostic test preference.

2.5. Statistical Analysis

We performed a sample size calculation based on previous pediatric ambulatory sleep studies without capnography that reported a sensitivity of 75-100% for OSA[15–18]. 37 children achieved 80% power to detect a sensitivity of 90% with an estimated precision of 9%.

We report descriptive statistics (median and interquartile range (IQR) and counts and proportions) to summarize demographic and clinical data. We used Student's t-tests to compare continuous parametric data (total sleep time with $tcCO_s$ >50 mmHg), and the Wilcoxon Mann-Whitney U test for nonparametric data (all other data). Distribution normality was determined using the Shapiro-Wilk test and visual inspection methods.

We calculated sensitivity, specificity, 95th percentile confidence intervals (CI), positive and negative predictive values, and diagnostic accuracy. We generated a receiver operating curve (ROC) using the two definitions of nocturnal hypoventilation as cut-points and calculated the area under the curve (AUC) to determine the discriminative ability of ambulatory $tcCO_2$ monitoring as a diagnostic test. We used Cohen's kappa to assess the agreement between ambulatory $tcCO_2$ and PSG $tcCO_2$ studies and PSG $etCO_2$ and PSG $tcCO_2$. We used the Spearman's Rho test due to non-normal distribution of data to determine correlations between mean $tcCO_2$ for ambulatory and PSG study parameters. Lastly, we generated Bland-Altman plots to analyse the agreement between tests. Analyses were performed using R Studio (2021.09.1+372).

2.6. **Ethical Considerations**

This study was approved by the SickKids Research Ethics Board, Toronto, Canada (REB 1000012349242). The study was registered with ClinicalTrials.gov (NCT03478566).

3. RESULTS

3.1. Baseline Characteristics

We enrolled 39 participants. Three had unusable ambulatory $tcCO_2$ data due to failure of drift correction on the machine (n=2) or an air bubble (n=1). All patients had PSG $tcCO_2$ data, whereas 3 patients had missing PSG $etCO_2$ data because of intolerance of application of the nasal sensor. The median (IQR) age of the remaining 36 participants was 12.5 (6.0-15.8) years. Patients lived a median of 41.5 km (IQR 23.3-61.8) away from the hospital and sleep laboratory. Baseline clinical characteristics are described in Table 1.

3.2. Comparison of Level 1 Polysomnography vs. Ambulatory $tcCO_2$ Results

Table 2 reports level 1 PSG and ambulatory $tcCO_2$ study results. Median (IQR) time between ambulatory $tcCO_2$ and PSG was 10.5 days (5.0-20.8 days).

Using AASM criteria, 2 children (5.6%) met criteria for nocturnal hypoventilation using PSG $etCO_2$, 5 (13.9%) met criteria using PSG $tcCO_2$, and 3 (8.3%) met criteria using ambulatory $tcCO_2$ measurements[12]. Using DMD specific criteria, 8 children (22.2%) met criteria for nocturnal hypoventilation using PSG $etCO_2$, 8 (22.2%) met criteria using PSG $tcCO_2$, and 6 (16.7%) met criteria using ambulatory $tcCO_2$ measurements [13].

3.3. Diagnostic Accuracy of Ambulatory $tcCO_2$ Monitoring

Using the diagnostic criteria for nocturnal hypoventilation of CO_2 >50mmHg for ≥ 25% of the night, when comparing to the gold standard PSG we found ambulatory $tcCO_2$ to have a sensitivity of 0.0% (95% CI 0.0-84.2%) and specificity of 91.2% (95% CI 76.3-98.1%) (Table 3). When comparing ambulatory $tcCO_2$ to PSG $tcCO_2$ sensitivity was 20.0% (95% CI 0.5-71.6%) and specificity 93.5% (95% CI 78.6-99.2%) (Table 3).

When using the DMD Working Group criterion for nocturnal hypoventilation of CO_2 >50mmHg for ≥ 2% of the night, compared to PSG $tcCO_2$, ambulatory $tcCO_2$ sensitivity was 25.0% (95% CI 3.2-65.1%); specificity 85.7% (95% CI 67.3-96.0%) (Table 4). Compared to PSG $etCO_2$, ambulatory $tcCO_2$ sensitivity was 25.0% (95% CI 3.2-65.1%); specificity 85.7% (95% CI 67.3-96.0%) (Table 4).

The ROC curve for the two definitions of nocturnal hypoventilation as cut-points is shown in Figure 1. The AUC was 0.595 indicating poor discrimination.

3.4. Agreement Between Level 1 Polysomnography and Ambulatory $tcCO_2$ Monitoring

There was no agreement between the ambulatory mean $tcCO_2$ measurements and the PSG $etCO_2$ measurements, with a kappa coefficient of -0.07 (SE 0.03; 95% CI -0.1 to -0.003). There was only slight agreement between the mean $tcCO_2$ measurements from the ambulatory and PSG studies, with a kappa coefficient of 0.2 (SE 0.2; 95% CI -0.5 to 0.5).

3.5. Correlation Between Level 1 Polysomnography and Ambulatory $tcCO_2$ Monitoring

There was poor correlation between the ambulatory mean $tcCO_2$ measurements and the PSG $etCO_2$ measurements (r= 0.2; 95^{th} CI -0.1-0.5; p=0.2). Similarly, mean $tcCO_2$ measurements from the ambulatory and PSG studies were also not found to be significantly correlated (r= 0.3; 95^{th} CI -0.1-0.5; p=0.1). There was also poor correlation between minimum ambulatory $tcCO_2$ and PSG $etCO_2$ measurements (r= 0.2; 95^{th} CI -0.2-0.5; p=0.3), maximum ambulatory $tcCO_2$ and

PSG $etCO_2$ measurements (r= 0.2; 95th CI -0.2-0.5; p=0.2), time spent >50 mmHg (r= 0.1; 95th CI -0.2-0.4; p=0.6), and percentage of time spent >50 mmHg (r= -0.03; 95th CI -0.4-0.3; p=0.8).

3.6 Bland-Altman Plots Comparing Level 1 Polysomnography and Ambulatory $tcCO_2$ Monitoring

Bland-Altman plots were generated to assess the agreement between ambulatory mean $tcCO_2$ measurements and the PSG $etCO_2$ measurements (Figure 2) and PSG $tcCO_2$ measurements (Figure 3). Overall, there was poor agreement between the ambulatory and PSG measurements.

3.7. Patient Experience

The median (IQR) patient comfort level during the ambulatory $tcCO_2$ study was 8 (8-10). Almost all participants (or parent) (34/36, 94%) preferred ambulatory monitoring over in-hospital PSG. The two patients who preferred PSG monitoring did not leave comment explaining their preference.

4. DISCUSSION

Accurate and early diagnosis and treatment of nocturnal hypoventilation is paramount to slow the development of diurnal hypercapnia, the leading cause of hospitalization and mortality for these children[1]. Our results indicate that current technology for ambulatory $tcCO_2$ monitoring has limited diagnostic accuracy for nocturnal hypoventilation in a cohort of children with NMD.

To our knowledge, our study is the first to evaluate the diagnostic accuracy of ambulatory $tcCO_2$ monitoring compared to the gold standard PSG in children with NMD. To date, two studies have

evaluated overnight home tcCO2 monitoring in children. Felemban et al. compared overnight $tcCO_2$ and pulse oximetry recordings performed at home and in-hospital in a cohort of 11 children with NMD and 13 children with other disorders treated with long-term NIV[11]. Mean values for at home and in-hospital $tcCO_2$ measurements were comparable to those in our study[11]. Another study by Griffon et al. analysed $tcCO_2$ recordings of children treated with or weaned from continuous positive airway pressure (CPAP), NIV or high flow nasal oxygen[12]. Data, however, were not compared to any in-hospital measurements, and neither of these studies evaluated diagnostic accuracy.

End-tidal capnography has also been previously studied in the ambulatory setting with albeit limited success. Fishman and colleagues demonstrated that an ambulatory level III PSG study with $etCO_2$ similarly had only moderate diagnostic accuracy (sensitivity and specificity to detect SDB was 61.5% and 86.7%, respectively) when compared to a level I PSG. Misinterpretation of falsely high or falsely low measurements can lead to potential mismanagement of these already complex and vulnerable children. As such, our results are congruent with others highlighting the need for increased allocation of healthcare funding for gold standard level I PSG testing to diagnose nocturnal hypoventilation in children with NMD given the existing limitations with ambulatory studies at present[19].

The same brand of tcCO2 machines were used for both the PSGs as well as the ambulatory studies. Three participants were excluded due to unusable ambulatory $tcCO_2$ data. Obtaining accurate $tcCO_2$ recordings can be technically challenging and labour intensive. The sensor probe is sensitive to temperature, and the heated probe may cause thermal injury (e.g. blisters, burns)[20].

Falsely elevated $tcCO_2$ measurements can result from increased capillary blood flow and low temperature, while falsely low $tcCO_2$ levels can result from a hypo-perfused state, skin edema or sweat, an air bubble in the sensor, or excessive contact gel[20]. Because of these pitfalls, the device requires continuous calibration during PSG. A potential solution would be the performance of the ambulatory test under the supervision of a trained technologist or RT for its duration; however, this would negate some of the cost- and resource-saving goals of ambulatory testing. Therefore, the ambulatory tcCO2 monitor likely requires further technological advancement resulting in increased ease of use before it can be used in the pediatric ambulatory setting. Overall, in its current state, with limited diagnostic accuracy and feasibility in the home setting, ambulatory $tcCO_2$ monitoring is unfortunately not yet able to save the long distance that many families need to travel to reach the formal sleep laboratory.

There were a few notable limitations to our study. First, our study was likely underpowered as only five study participants had a PSG diagnosis of nocturnal hypoventilation. The presence of hypoventilation was not an inclusion criterion as we took a pragmatic approach to studying a cohort of children referred to our sleep laboratory for evaluation of SDB. Therefore, there is a need for future studies to investigate the utility of ambulatory $tcCO_2$ monitoring in a pediatric and adult cohort with a higher prevalence of nocturnal hypoventilation. Second, for our evaluation of diagnostic accuracy, we compared ambulatory $tcCO_2$ to $etCO_2$ recordings during PSG rather than arterial blood gas (ABG) for two reasons. Firstly, this was done for ease of collection for the child. Second, technically comparing one continuous CO_2 data recording to another continuous recording was chosen rather than to an ABG, a single time point measurement, given the known variability of CO_2 levels overnight with progression through

sleep stages. Third, ambulatory $tcCO_2$ used total recording time instead of total sleep time which may have inflated the denominator for calculating the percentage of time spent with $tcCO_2$ >50 mmHg. This inability to accurately capture TST is a well-described limitation of home sleep apnea tests. Potential proposed solutions include adding additional leads (ECG, respiratory effort monitoring) to quantify sleep using autonomic physiology, or recording subjective TST, though this is also commonly inaccurate[21]. As there are currently no well-established methods of accurately determining TST from home sleep testing, the underestimation of TST remains a risk as it can lead to the under detection of sleep-disordered breathing and hypoventilation, which in turn can affect therapeutic decision making and patient care.

5. CONCLUSION

Although ambulatory $tcCO_2$ monitoring appears to be well tolerated and preferred by patients and families, it is not yet a practical clinical tool for the diagnosis of nocturnal hypoventilation in children with NMD due to its low diagnostic accuracy and technical challenges in the home setting. Future directions for this work include an evaluation of diagnostic accuracy of ambulatory $tcCO_2$ compared to PSG in a cohort of children and/or adults with established hypoventilation.

REFERENCES

1. Eagle M, Baudouin S V., Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: Improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord*. 2002;12(10):926-929. doi:10.1016/S0960-8966(02)00140-2
2. Wise MS, Nichols CD, Grigg-Damberger MM, et al. Executive summary of respiratory indications for polysomnography in children: An evidence-based review. *Sleep*. 2011;34(3):389-398. doi:10.1093/sleep/34.3.389
3. Katz SL, Witmans M, Barrowman N, et al. Paediatric sleep resources in Canada: The scope of the problem. *Paediatr Child Health*. 2014;19(7):367-372. doi:10.1093/pch/19.7.367
4. Aboussouan LS. Sleep-disordered breathing in neuromuscular disease. *Am J Respir Crit Care Med*. 2015;191(9):979-989. doi:10.1164/rccm.201412-2224CI
5. Labanowski M, Schmidt-Nowara W, Guilleminault C. Sleep and neuromuscular disease: Frequency of sleep-disordered breathing in a neuromuscular disease clinic population. *Neurology*. 1996;47(5):1173-1180. doi:10.1212/WNL.47.5.1173
6. Chiang J, Mehta K, Amin R. Respiratory Diagnostic Tools in Neuromuscular Disease. *Children*. 2018;5(6):78. doi:10.3390/children5060078
7. Annane D, Orlikowski D, Chevret S. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Syst Rev*. 2014;2014(12). doi:10.1002/14651858.CD001941.pub3
8. Hull J, Aniapravan R, Chan E, et al. British Thoracic Society guideline for respiratory

management of children with neuromuscular weakness. *Thorax*. 2012;67(Suppl 1):i1-i40. doi:10.1136/thoraxjnl-2012-201964

9. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with duchenne muscular dystrophy: ATS consensus statement. In: *American Journal of Respiratory and Critical Care Medicine*. Vol 170. Am J Respir Crit Care Med; 2004:456-465. doi:10.1164/rccm.200307-885ST
10. Suresh S, Wales P, Dakin C, Harris MA, Cooper DM. Sleep-related breathing disorder in Duchenne muscular dystrophy: Disease spectrum in the paediatric population. *J Paediatr Child Health*. 2005;41(9-10):500-503. doi:10.1111/j.1440-1754.2005.00691.x
11. Felemban O, Leroux K, Aubertin G, et al. Value of gas exchange recording at home in children receiving non-invasive ventilation. *Pediatr Pulmonol*. 2011;46(8):802-808. doi:10.1002/ppul.21427
12. Griffon L, Touil S, Frapin A, Khirani S, Amaddeo A, Fauroux B. Home monitoring of transcutaneous PCO2 in children on long term ventilation. In: *European Respiratory Journal*. Vol 52. European Respiratory Society (ERS); 2018:PA2382. doi:10.1183/13993003.congress-2018.pa2382
13. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: Update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med*. 2012;8(5):597-619. doi:10.5664/jcsm.2172
14. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17(4):347-361. doi:10.1016/S1474-4422(18)30025-5
15. Lesser DJ, Haddad GG, Bush RA, Pian MS. The utility of a portable recording device for

screening of obstructive sleep apnea in obese adolescents. *J Clin Sleep Med*. 2012;8(3):271-277. doi:10.5664/jcsm.1912

16. Massicotte C, Al-Saleh S, Witmans M, Narang I. The utility of a portable sleep monitor to diagnose sleep-disordered breathing in a pediatric population. *Can Respir J*. 2014;21(1):31-35. doi:10.1155/2014/271061

17. Zucconi M, Calori G, Castronovo V, Ferini-Strambi L. Respiratory monitoring by means of an unattended device in children with suspected uncomplicated obstructive sleep apnea: A validation study. *Chest*. 2003;124(2):602-607. doi:10.1378/chest.124.2.602

18. Jacob S V., Morielli A, Mograss MA, Ducharme FM, Schloss MD, Brouillette RT. Home testing for pediatric obstructive sleep apnea syndrome secondary to adenotonsillar hypertrophy. *Pediatr Pulmonol*. 1995;20(4):241-252. doi:10.1002/ppul.1950200407

19. Fishman H, Massicotte C, Li R, et al. The Accuracy of an Ambulatory Level III Sleep Study Compared to a Level I Sleep Study for the Diagnosis of Sleep-Disordered Breathing in Children With Neuromuscular Disease. *J Clin Sleep Med*. 2018;14(12):2013-2020. doi:10.5664/jcsm.7526

20. Restrepo RD, Hirst KR, Wittnebel L, Wettstein R. AARC clinical practice guideline: Transcutaneous monitoring of carbon dioxide and oxygen: 2012. *Respir Care*. 2012;57(11):1955-1962. doi:10.4187/respcare.02011

Table 1: Baseline Characteristics of the Study Cohort

Characteristic (N=36)	
Age (years)	12.5 (6.0-15.8)
Female sex	11 (31)
Body mass index (kg/m^2)	19.2 (15.0-23.1)
Distance from hospital (km)	41.5 (23.3-61.8)
Forced vital capacity (% predicted)	69.0 (55.0-77.0)
Diagnosis	
Duchenne muscular dystrophy	13 (36.1)
Congenital myopathy	6 (16.7)
Congenital muscular dystrophy	5 (13.9)
Spinal muscular atrophy type I	2 (5.6)
Spinal muscular atrophy type II	1 (2.8)
Spinal muscular atrophy type III	2 (5.6)
Juvenile amyotrophic lateral sclerosis	2 (5.6)
Neuromuscular disease NYD	2 (5.6)
Myasthenia gravis	1 (2.8)
Ataxia-telangiectasia	1 (2.8)
Becker muscular dystrophy	1 (2.8)

Data are either presented as median (interquartile range [IQR]) or number (percentage). Forced vital capacity (FVC) was able to be completed in 26 patients. IQR = interquartile range. NYD = not yet determined.

Table 2: Level I Polysomnography and Ambulatory Transcutaneous Carbon Dioxide Monitoring Results

Characteristic	Level I PSG	Ambulatory $tcCO_2$ Monitor	P-value
Recording time (minutes)	454.3 (430.6-502.1)	580.5 (528.5-644.8)	<0.0001
Total sleep time (minutes)	387.0 (399.5-414.0)	N/A	
Transcutaneous CO_2 (mmHg)			
Minimum	36.5 (32.0-41.0)	36.1 (32.8-38.4)	0.6
Maximum	47.5 (43.0-51.8)	45.7 (43.9-49.5)	0.6
Mean	43.5 (39.3-47.0)	42.5 (40.0-45.3)	0.6
Time >50 mmHg (minutes)	35.6 (85.9)	29.6 (92.3)	0.6
%Time >50 mmHg	9.2 (22.6)	5.9 (19.0)	0.7
End-tidal CO_2 (mmHg)			
Minimum	28.0 (25.5-32.0)	N/A	<0.001*
Maximum	51.0 (46.0-54.0)	N/A	0.2*
Mean	43.0 (40.3-44.5)	N/A	0.7*
Time >50 mmHg (minutes)	17.5 (50.2)	N/A	0.9*
%Time >50 mmHg	4.4 (12.5)	N/A	0.7*
OAHI (events/h)	1.4 (0.3-5.4)	N/A	
CAHI (events/h)	0.9 (0.3-1.7)	N/A	
Hypoventilation – AASM[+]			
Using $tcCO_2$	5 (13.9%)	3 (8.3)	
Using $etCO_2$	2 (5.6%)	N/A	
Hypoventilation – DMD[++]			
Using $tcCO_2$	8 (22.2%)	6 (16.7)	
Using $etCO_2$	8 (22.2%)	N/A	

Data are either presented as median (interquartile range [IQR]), mean (standard deviation [SD]), or number (percentage).
OAHI = obstructive apnea-hypopnea index. CAHI = central apnea-hypopnea index. CO_2 = carbon dioxide. $tcCO_2$ = transcutaneous CO_2. DMD = Duchenne Muscular Dystrophy
*p-value comparing end-tidal CO_2 from PSG to $tcCO_2$ from ambulatory study.
[+]Nocturnal hypoventilation as defined by a CO_2 recording >50mmHg for ≥ 25% of the night.
[++] Nocturnal hypoventilation as defined by a CO_2 recording >50mmHg for ≥ 2% of the night, using 2018 Duchenne Muscular Dystrophy (DMD) Care Considerations Working Group[13].

Table 3: Sensitivity and Specificity of Ambulatory $tcCO_2$ Monitoring compared to Polysomnography $etCO_2$ and $tcCO_2$ Measurements using AASM Criteria

	Comparison to PSG $etCO_2$ (95^{th} CI)	Comparison to PSG $tcCO_2$ (95^{th} CI)
Sensitivity	0.0% (0.0-84.2%)	20.0% (0.5-71.6%)
Specificity	91.2% (76.3-98.1%)	93.6% (78.6-99.2%)
Positive Predictive Value	0	33.3% (5.2-82.0%)
Negative Predictive Value	93.9 % (93.3-94.5%)	87.9% (82.3-91.9%)
Accuracy	86.1 (70.5-95.3)	83.3 (67.2-93.6)

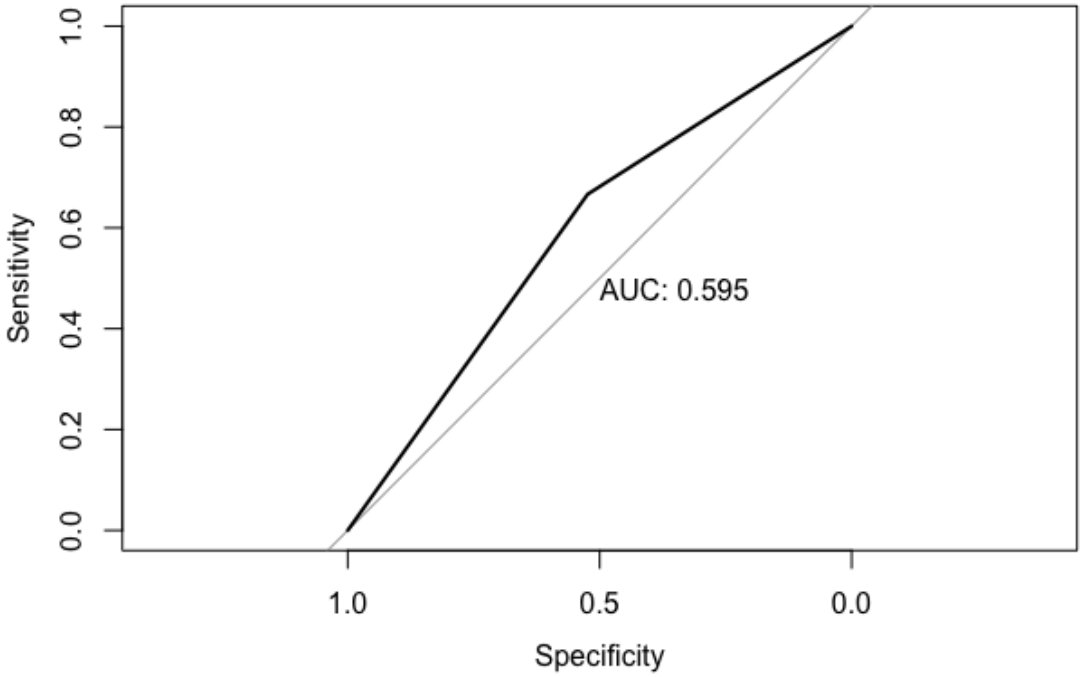
$tcCO_2$ = transcutaneous carbon dioxide; $etcCO_2$ = end-tidal carbon dioxide; CI = confidence interval.
American Academy of Sleep Medicine criteria: Nocturnal hypoventilation as defined by a CO_2 recording >50mmHg for ≥ 25% of the night[12].

Table 4: Sensitivity and Specificity of Ambulatory $tcCO_2$ Monitoring compared to Polysomnography $etCO_2$ and $tcCO_2$ Measurements using DMD Specific Criteria

	Comparison to PSG $etCO_2$ (95^{th} CI)	Comparison to PSG $tcCO_2$ (95^{th} CI)
Sensitivity	25.0% (3.2-65.1%)	25.0% (3.2-65.1%)
Specificity	85.7% (67.3-96.0%)	85.7% (67.3-96.0%)
Positive Predictive Value	33.3% (10.0-69.2%)	33.3% (10.0-69.2%)
Negative Predictive Value	80.0% (72.3-86.0%)	80.0% (72.3-86.0%)
Accuracy	72.2 (54.8-85.8)	72.2 (54.8-85.8)

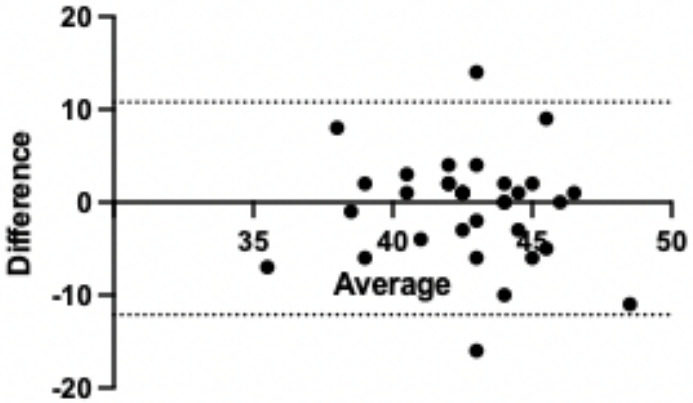
$tcCO_2$ = transcutaneous carbon dioxide; $etcCO_2$ = end-tidal carbon dioxide; CI = confidence interval.
Duchenne Muscular Dystrophy specific criteria: Nocturnal hypoventilation as defined by a CO_2 recording >50mmHg for ≥ 2% of the night[13].

Figure 1: Receiver Operating Characteristic Curve for Ambulatory $tcCO_2$ Monitoring



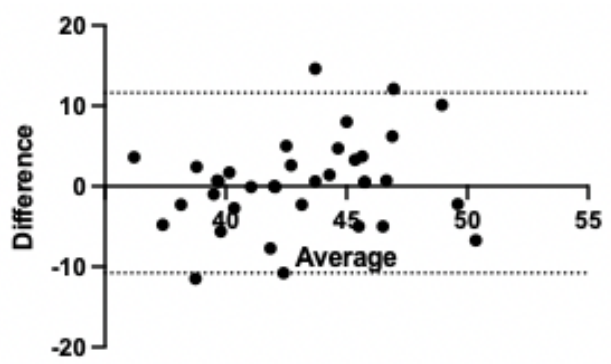
$tcCO_2$ = transcutaneous carbon dioxide; AUC= area under the curve.

Figure 2: Bland-Altman Plot comparing Ambulatory $tcCO_2$ Monitoring against Polysomnography $etCO_2$



Bias 0.4 mmHg, SD 5.7 mmHg
Dotted line = bias, dashed lines = 95% limits of agreement

Figure 3: Bland-Altman Plot comparing Ambulatory $tcCO_2$ Monitoring against Polysomnography $tcCO_2$



Bias -0.7 mmHg, SD 5.8 mmHg
Dotted line = bias, dashed lines = 95% limits of agreement