Stability of Polysomnography for One Year and Longer in Children with Sickle Cell Disease

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Study Objectives: Serious morbidity may be linked to sleep disordered breathing (SDB) among children with sickle cell disease (SCD). We investigated the stability of polysomnography (PSG) results among children not having acute complications of SCD.

Methods: Two PSGs were performed on a subsample of 63 children 4 to 18 years of age from the Sleep and Asthma Cohort Study. All had Hb SS or HbSβ⁰ disease. Two PSGs were compared for 45 subjects. Excluded from comparison were 18 children who had begun transfusions or hydroxyurea, had an adenotonsillectomy between the PSGs, or had a pain crisis or the acute chest syndrome within 3 months of the second PSG. Sleep disordered breathing was identified using 2 thresholds for the apnea hypopnea index (AHI): ≥ 2 or ≥ 5 respiratory events per hour.

Results: Ages were $12.3 \text{ yrs} \pm 4.0$, BMI, 18.2 ± 3.2 . Interval

between PSGs was 581 ± 119 days (19.1 ± 3.9 months). Ten of 45 changed from ≥ 2 events per hour to < 2 ; 3 of 45 from < 2 to ≥ 2 ; 7 of 45 had ≥ 2 on both nights. Six of 45 changed from ≥ 5 to < 5 , 2 of 45 from < 5 to ≥ 5 , and 1 had ≥ 5 on both nights (McNemar χ^2 , $p = 0.09$, and $p = 0.29$).

Conclusions: In the absence of acute SCD complications, overnight PSG usually remains stable or improves over a 12- to 30-month period. Only 6.7% subjects, or fewer, had AHI on a subsequent PSG that would re-classify the child as having SDB not identified in the earlier PSG.

Keywords: Sickle cell disease, polysomnography, obstructive sleep apnea

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Obstructive sleep apnea (OSA) is more prevalent in children with sickle cell disease than in children without SCD.^{1,2} SDB has been linked to serious SCD-associated morbidity, including vaso-occlusive crises, pulmonary hypertension, and strokes.³⁻¹⁰ There are several possible causes for the high prevalence of OSA and other types of sleep disordered breathing among children with SCD—stroke, adenotonsillar hypertrophy, airway narrowing due to bone marrow hyperplasia,⁶ and the increased rate of OSA among African American children in general.¹¹

Among children with SCD, symptoms of sleep disordered breathing may be particularly unreliable—daytime sleepiness or behavioral problems may be due to sleep disruption by pain, pain treatment, or stroke. In addition, preliminary results suggest that more than 20% of SCD patients with sleep disordered breathing do not have habitual snoring.¹²

PSG is considered the “gold standard” test for evaluating SDB. However, it can be burdensome and its clinical value over a symptom-based classification for children with SCD has been debatable, because of a lack of data on the stability and interpretability of the findings. We investigated whether classification of SDB status changes 1 year or more after an initial PSG in a group of SCD patients who were clinically stable at

BRIEF SUMMARY

Current Knowledge/Study Rationale: Particularly serious morbidity is associated with sleep-disordered breathing among patients with sickle cell disease. We investigated whether polysomnography results would change in otherwise stable patients.

Study Impact: Over an 18 month interval, in the absence of worsening of symptoms due to sleep-disordered breathing or sickle cell disease, polysomnography results were stable among patients 4 to 18 years old.

both the first and second study. To our knowledge, no studies have compared the *stability* of PSG results over long intervals in children, although short-term variability, or reproducibility, has been addressed.

We examined PSG from participants in the prospective, multicenter Sleep and Asthma Cohort (SAC) Study. In this report we evaluated the stability of the respiratory PSG parameters measured after a 12- to 30-month interval. Specifically, among children with SCD who were not selected for any respiratory signs or complaints, we tested the hypothesis that there would be no significant difference in selected respiratory parameters between two sleep studies, done one year or more apart.

METHODS

Institutional review board approval was obtained at Washington University in St. Louis, Missouri, and Case Medical Center, Cleveland, Ohio.

Participants

Participants were excluded from this study if they met any of the following criteria: chronic blood transfusion at time of enrollment, comorbidities such as Pierre-Robin sequence, craniosynostosis, neuromuscular disease, serious preexisting lung disease, or use of continuous positive airway pressure therapy. Patients were not excluded if they had adenotonsillar hypertrophy or prior adenoid or tonsil surgery. A PSG was performed upon enrollment for all patients, provided they were free of pain or symptoms of a respiratory infection. A second PSG was performed later on a convenience sample of 63 patients willing to undergo a second study enrolled at 2 of the 3 SAC sites (St. Louis and Cleveland), when they were free of pain or symptoms of a respiratory infection.

Participants were ≥ 4 and ≤ 18 years old with sickle cell disease: Hemoglobin SS or Hemoglobin HbS β^0 Thalassemia (Hb SS or HbS β^0). Participants who were prescribed hydroxyurea, or had an adenoidectomy, tonsillectomy, or adenotonsillectomy between studies underwent the second PSG but were excluded from this analysis. Any participant requiring supplemental oxygen during a PSG, as determined by clinician's judgment, was excluded from the analysis. Medical records were reviewed to determine which participants were hospitalized for vaso-occlusive pain events or acute chest syndrome within 3 months of a PSG, which participants were hospitalized for respiratory symptoms within 2 weeks of a PSG, and which participants were started on chronic blood transfusion between PSGs. These participants were also excluded from the analysis. None were excluded because of worsening symptoms of OSA between PSGs—snoring, behavioral disturbances, daytime sleepiness, etc. Analgesic drugs were routinely prescribed for as needed use. Frequencies of narcotic use or prescription refills were not analyzed.

Polysomnography

Each patient underwent 2 nocturnal PSGs in the sleep laboratories at St. Louis Children's Hospital/Washington University in St. Louis or the clinical research unit at University Hospital–Case Medical Center, Cleveland, Ohio. The PSGs were performed using a standardized protocol and centrally scored at a reading center by research polysomnologists who were blinded to any clinical data, per the SAC protocol as described in detail elsewhere.¹³ Inter- and intra-scorer reliability were monitored across the study and demonstrated to be excellent for all PSG parameters. Any clinical management decisions made based on the initial study were according to the standards of care at each site.

Obstructive apneas were identified when there was absent nasal-oral airflow by thermistor with continued respiratory effort lasting ≥ 5 sec and 2 missed breaths, regardless of associated desaturation. Hypopneas were scored when there was a 50% reduction in airflow by nasal pressure or 50% reduction in volume by the sum signal from thoracic and abdominal inductance plethysmography and $\geq 3\%$ desaturation continuing for

≥ 5 sec and 2 missed breaths. The obstructive apnea hypopnea index with 3% desaturation (AHI) was defined as the number of obstructive apneas with or without desaturations plus hypopnea events associated with 3% desaturation per hour of sleep.

The prevalence of SDB was assessed using 2 different frequency thresholds of the AHI: ≥ 2 events/h, and ≥ 5 events/h. These thresholds were chosen to approximate conservative thresholds for SDB proposed for children younger than or older than 12 years of age.

Continuous measures of hemoglobin oxygen saturation levels (SpO₂ %) were further described for each subject in terms of percent total sleep time levels of oxyhemoglobin saturation of $< 95\%$ and $< 90\%$.

Data Analysis

Other PSG indices analyzed included total sleep time (TST), percent of TST in REM sleep, percent of TST in the supine position, AHI, and average SpO₂ % during sleep. Study 1 and Study 2 group-mean differences were compared using unpaired *t* tests or the Mann-Whitney rank-sum test. The within-subject differences of key variables were compared between nights using paired *t* tests for normally distributed variables and Wilcoxon signed-rank test for variables that were not distributed normally. Difference values were calculated subtracting Study 1 values from Study 2. All point estimates are presented with 95% confidence intervals unless otherwise indicated.

Further analysis was conducted for the primary metric of AHI. Participants were classified as having SDB using both thresholds (≥ 2 and ≥ 5 events/h) and were classified into 4 groups based on congruency of classification from Study 1 to Study 2: no SDB on both nights, SDB on study 1 only, SDB on study 2 only, and SDB on both nights. Analysis of variance (ANOVA) was conducted on all 4 groups to compare the groups on the basis of age at date of first study, number of days between studies, BMI, time spent in REM sleep, time spent supine, and difference in time spent in REM sleep and in time spent supine. Chi-square analyses were used to compare all 4 groups on the basis of site and gender, using Fisher exact test when appropriate. McNemar test for changes was used to quantify the significance of changes in category (SDB vs. no SDB) from night 1 to night 2, using both ≥ 2 and ≥ 5 event thresholds.

RESULTS

Patient Characteristics

Sixty-three children had 2 PSGs performed an average of 581 [544.7, 616.4] days apart (range: 322–987 days or 10.6 to 32.4 months). Forty-five participants met the inclusion criteria for analysis of both PSGs in this study. Eighteen were excluded because they had begun transfusions (8), hydroxyurea (4), or nighttime supplemental oxygen (1), had an adenotonsillectomy between PSGs (1), or had a pain crisis or acute chest syndrome (4) within 3 months before the second PSG. Five participants were taking hydroxyurea at the time of both PSGs, and were included in the final analysis. Mean age at time of first study was 12.3 [11.1, 13.5] years (range: 4.6–18.7), and 49% were male. Mean BMI on night of study 1 was 18.2 [17.3, 19.2] kg/

Table 1—Group mean results for sleep and respiratory parameters for PSG nights 1 and 2

	Night 1 (mean [95% CI])	Difference night 2 – night 1 (mean [95% CI])	P value
Sleep variables			
Total Sleep Time (min)	473.4 [451.0, 495.8]	45.4 [22.4, 68.4]	< 0.001
REM (%TST)	19.2 [17.2, 21.2]	1.4 [-1.0, 3.7]	0.226
Supine position (%TST)	47.3 [40.3, 54.3]	3.0 [-5.1, 11.2]	0.453
Respiratory variables			
AHI	1.2 [0, 35.2]*	-1.45 [-3.2, 0.3]	0.154
Average SpO ₂ % during sleep	94.5 [93.6, 95.5]	0.4 [-0.5, 1.3]	0.487

*Median and Range values, respectively.

m² (range: 14.1-27.7) and 19.1 [18.2, 20.1] (14.7-27.8) on night 2. The change in BMI was not significant, (0.9 [-0.4, 1.3])

Comparison of Group Mean PSG Parameters between Study 1 and Study 2

(Table 1) Mean difference of AHI between study 2 and study 1 was 1.45 [-0.3, 3.2] and mean difference of average SpO₂ between study 2 and study 1 was -0.4 [-1.3, 0.5]. Mean difference of total sleep time between night 2 and 1 was 45.4 [22.4, 68.4] minutes. Mean difference of time in REM sleep and time in the supine position (as a percent of total sleep time) between night 2 and 1 was, respectively, 1.4 [-1.0, 3.7] and 3.0 [-5.1, 11.2]. Except for total sleep time, there were no significant group mean differences between first and second PSG.

Polysomnographic classification of SDB remained consistent for both thresholds

The relationship between difference in AHI (night 2 – night 1) and mean AHI (for night 1 plus night 2) for each subject is depicted in Figure 1. One participant with a mean AHI of 7 had 7 more events on night 2 than on night 1. All other participants with large differences had fewer events on night 2 (Figure 1).

(Table 2) Using AHI with a threshold of 2 events/h, 28.8% (13/45) of the participants changed categories between the 2 studies. A total of 22.2% (10/45) went from ≥ 2 events/h on study night 1 to < 2 events/h on study night 2, and 6.7% (3/45) went from < 2 events/h on study 1 to ≥ 2 events/h on study 2; 15.6% (7/45) had ≥ 2 events/hour on both nights. There was no difference between any of the 4 of these groups (neg-neg, neg-pos, pos-neg, pos-pos) with respect to age, gender, BMI, site, or days between PSG.

(Table 3) Using AHI with a threshold of 5 events/h, 17.8% (8/45) of the participants changed categories between the 2 studies: 13.3% (6/45) went from ≥ 5 events/h on night of study 1 to < 5 events/h on night of study 2, and 4.4% (2/45) went from < 5 events/h on night of study 1 to ≥ 5 events/h on study 2. Only 1/45 (2.2%) had ≥ 5 events/h on both nights. Again, there was no difference between any of the 4 of these groups (neg-neg,

Figure 1—Relationship between mean AHI index for both PSGs and difference in AHI (Study 2 – Study 1) is depicted in the Bland-Altman Plot

One subject had an AHI of 35 on the first PSG, but only 1 event/h on the second. His results are not shown in the plot.

Table 2—AHI threshold of 2 events/hour

Night 2	Night of Study 1	
	≥ 2	< 2
≥ 2	7	3
< 2	10	25

Table 3—AHI threshold of 5 events/hour

Night 2	Night of Study 1	
	≥ 5	< 5
≥ 5	1	2
< 5	6	36

neg-pos, pos-neg, pos-pos) with respect to age, gender, BMI, site, or days between PSG.

Changes in classification from night 1 to night 2, for both thresholds, were not significant (McNemar test for changes, McNemar χ^2 , 3.77 and 2.00, $p = 0.09$, and $p = 0.29$, respectively.)

For all subjects, regardless of SDB classification, the average total sleep time with SpO₂% $< 90\%$ was 8.9% on study night 1 and 4.7% on study night 2; the average sleep time with SpO₂% $< 95\%$ was 47.3% on study night 1 and 50.0% on study night 2. Individuals did not differ significantly on paired t -tests in percent of total sleep time for oxyhemoglobin saturations $< 90\%$ on study night 1 vs. study night 2 ($p = 0.3560$) or in percent of total sleep time $< 95\%$ ($p = 0.5319$).

Among the 18 subjects who had 2 PSGs but whose results were excluded from the group comparisons, 6 of 18 (33%) had AHI ≥ 2 on study night 1, and 2 of 18 (11%) had AHI ≥ 5 . On study night 2, 1 of 18 (6%) had AHI ≥ 2 and none had AHI ≥ 5 . Though not explored in detail, this reduction in SDB sever-

ity on the second exam is consistent with the more aggressive treatment for SCD these children received.

DISCUSSION

Because of severe morbidity associated with SDB, an argument could be made to do routine second PSGs as screening tests on children with SCD, even in the absence of progression of symptoms of SDB or abnormalities on the first PSG. Our study showed that among children studied when free of acute illness and not receiving specific treatment for SDB or more aggressive SCD therapy, classification of SDB changed little over an average of 1.5 years. Specifically, using either of two alternative definitions of SDB, most children who were not classified with SDB on the first PSG also were free of SDB later. In contrast, despite an insignificant increase in BMI and without surgical intervention, when the PSG was abnormal on night of study 1, 59% to 86% subsequently had results below the threshold on night of study 2 (< 2 or < 5 events/h, 10 of 17, or 6 of 7, respectively).

The question of which children with SCD to study with PSG, and the frequency of study, is unsettled. In any child with a chronic health condition, changes in overall health, medication use, lung function, nasal congestion, and body weight and other factors all may influence the measured severity of SDB at any given point in time. Furthermore, interpreting PSG in children with SCD can be challenging due to underlying abnormalities in lung function and in oxyhemoglobin saturation, which can obscure the identification of hypopneas among subjects whose hemoglobin has less affinity for oxygen than Hgb A. The results of the current study suggest that a PSG performed when children with SCD were free of acute illness provided an estimate of SDB severity that changes little over 1.5 years. In particular, very few children whose first PSG results were below recognized thresholds for SDB developed new SDB over this period of time. On the other hand, some children with AHI above SDB threshold values were measured to have lower AHIs at a later point. This may be due to a reduction in SDB severity with growth in children (reflecting a relative increase in airway size over tonsillar mass) or could reflect a "regression to the mean." However, even with the latter reclassification, the overall mean change in AHI as well as other PSG parameters were modest, suggesting that for research purposes, a single PSG performed under the appropriate conditions may provide reliable estimates of SDB in children not undergoing interventions that could alter SDB severity.

How less inconvenient or labor-intensive proxies for full PSG might be used in children with SCD deserves attention. However, as noted above, particular caution must be taken when applying methods to assess hypopnea primarily based on $SpO_2\%$ in patients whose hemoglobin may have unpredictable affinity for oxygen.

Other caveats seem important to the prudent use of our findings. Although less frequently than in children without SCD, habitual snoring, labored breathing, and apnea are associated with SDB among children with SCD,¹² and thus a worsening in these symptoms should prompt consideration to repeat the PSG. Even though our findings showed little progression of disease within subjects who did not undergo adenotonsillectomy,

these findings should not alter current approaches that demand that progression of symptoms of SDB warrants re-evaluation of SDB.

There are several other limitations. First the subjects were a convenience sample from the Sleep and Asthma Cohort. Second, we excluded from analysis patients receiving chronic transfusion therapy and those begun on hydroxyurea between the PSG. Our results are thus most pertinent to patients with less severe SCD and to those who may be using hydroxyurea but not recently begun on this agent. Finally, we did not compare symptoms of SDB before Study 1 to the appearance or progression of symptoms before Study 2. However, of 18 children excluded from comparison, only 1 was excluded because of an adenotonsillectomy between PSGs. Furthermore, only 4.4% to 6.7% of those with a normal PSG on Study 1 surpassed either threshold for SDB on Study 2. This suggests that even if more subjects were snoring or sleepy or had behavioral disturbances that a new classification as SDB would be unlikely.

Most studies on the reproducibility of PSG results in diagnosing OSA have focused on short-term variability. Studies in healthy adults have shown some modest night-to-night variability when the PSGs were performed at intervals < 28 days.¹⁴ Reproducibility of PSG results in children has been assessed in a small number of studies.¹⁵⁻¹⁷ In one study of children who snored, subjects had PSGs performed 7 to 28 days apart. The classification of OSA or primary snoring remained the same for all 30 participants.¹⁶

We did not examine the *short-term variability, or reproducibility*, of PSG in children with SCD. Rather, we have shown the *longer-term stability* of PSG in children with SCD who were free of vaso-occlusive crises or the acute chest syndrome for 3 months. In the absence of progression of pulmonary hypertension or new stroke, among children with SCD who are otherwise clinically stable, our results indicate that a second PSG 1 to 3 years after one that is normal is unlikely to show worsening sleep disordered breathing.

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