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SCIENTIFIC INVESTIGATIONS

Nocturnal hypoxemia measured by polysomnogram is associated with acute chest syndrome in pediatric sickle cell disease

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Study Objectives: Nocturnal hypoxemia is associated with increased risk of sickle cell disease (SCD) complications. The association of nighttime hypoxemia and acute chest syndrome (ACS) in children with SCD has yet to be determined.

Methods: This is a retrospective study of children with SCD who underwent polysomnography at a SCD center. Univariate logistic regression was used to assess the association between nocturnal hypoxemia and ACS admissions. Multivariate logistic regression was performed to verify the effects of different clinical covariates on ACS. Secondary analysis comparing patients with one vs multiple ACS admissions was performed.

Results: One hundred ten individuals with SCD who completed their polysomnogram (mean age of 9.4 years) were identified. Fifty-nine (54%) had a history of at least one episode of ACS admission (mean age of 4.1 years), including 40 with multiple episodes. The percentage of total sleep time with O_2 saturation < 90% was greater in the ACS group ($P < .05$). Similarly, mean nocturnal O_2 saturation was lower in the ACS group ($P < .0005$). Mean nocturnal O_2 saturation of < 97.3% and the percentage of total sleep time with O_2 saturation < 90% higher than 2.7% were associated with ACS. There was no difference in nocturnal hypoxemia between patients with single and multiple ACS admissions.

Conclusions: Nocturnal hypoxemia later in life is associated with previous ACS admissions in children with SCD. This can increase the yield of interpreting polysomnograms in this vulnerable population. Prospective studies are needed to determine the temporal relations of nocturnal hypoxemia and ACS, which may identify a modifiable risk for ACS.

Keywords: nocturnal; nighttime; hypoxia; acute chest syndrome; pediatric; sickle cell disease; sleep study; polysomnography; asthma.

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Hypoxemia induces red blood cells sickling in patients with sickle cell disease, leading to increased morbidity and mortality. Acute chest syndrome (ACS) is a leading cause of death in children with sickle cell disease, and most ACS risk factors are nonmodifiable. The association between nocturnal hypoxemia and ACS remains to be determined.

Study Impact: This study showed that nocturnal hypoxemia later in life is associated with previous ACS admissions in children with sickle cell disease. We determined cutoff points for two commonly used hypoxemia parameters in polysomnography that are associated with ACS, which will facilitate the interpretation of polysomnograms in sickle cell disease patients and direct prospective studies to confirm the temporal association to identify a modifiable risk factor for ACS.

INTRODUCTION

Sickle cell disease (SCD) is the most common inherited blood disorder in the United States affecting about 100,000 Americans and approximately 1 of every 365 African American.[1] Acute chest syndrome (ACS), the most devastating pulmonary complication seen in children with SCD, consists of a constellation of signs and symptoms characterized by dyspnea, cough, hypoxemia, chest pain, and fever. Clinically, ACS is diagnosed by the development of a new alveolar pulmonary infiltrate involving at least one lung segment.[2] It can progress to acute respiratory failure requiring intensive care admission and invasive interventions such as ventilation and exchange blood transfusion. ACS accounts for 25% of all deaths in patients with SCD, making it the leading cause of death in this population.[3] The current SCD guidelines by the American Society of Hematology identifies the relationship between sleep-disordered breathing and SCD outcomes as a specific area of need for research.[4]

Despite the great impact of ACS on SCD, the pathophysiology of ACS, risk factors, and treatment are largely unknown.[5] Few risk factors have been associated with ACS, such as genotype and history of asthma.[6] One potentially modifiable risk factor is hypoxemia, which serves as a strong trigger for erythrocyte sickling. Oxyhemoglobin desaturation is linked to several SCD complications, such as increased pain,[7] greater risk of central nervous system events,[8] and cognitive dysfunction.[9] Sleep-disordered breathing (SDB) can be associated with intermittent hypoxemia. Both SCD and SDB share common

pathogenic pathways, mainly ischemia and reperfusion injury with consequent hypoxia and reoxygenation. As a result, patients experience increased oxidative stress that triggers proinflammatory signaling cascades and induces autonomic instability, believed to play a major role in the morbidities associated with SCD and SDB.[10] Additionally, SDB has long been speculated to potentiate the complications of SCD; yet, the association between SDB and SCD remains largely unexplored.[10] Despite the fact that nocturnal hypoxemia has been strongly associated with increased neurological complications of SCD, especially stroke,[8,9] previous studies have not been able to clearly associate nocturnal hypoxemia with ACS. To date, only two prospective cohorts of children with SCD (95 and 140 patients) have assessed the influence of nighttime hypoxia on the development of vaso-occlusive crisis and ACS. Those studies demonstrated variable effects of nocturnal hypoxemia on vaso-occlusive events.[7,11] In the initial cohort, a 1% increase in the mean nocturnal O_2 saturation was associated with an average decrease of 0.83 days of pain per year; in the second cohort, this same increase was associated with a 10% increased rate of future pain episodes. No definitive association was noted in either study regarding nocturnal hypoxemia and the development of ACS. Of note, both studies included children with mean age of 10 years, whereas the peak incidence of ACS admissions occurs between 2 and 4 years of age.[12] This is a significant limitation given that ACS after the age of 4 years encompasses a broad spectrum of clinical conditions with likely different pathogeneses.[13,14] A second limitation in the field is that some of the previous studies used pulse oximetry to evaluate nighttime desaturation rather than the gold standard, the polysomnogram (PSG).[15,16]

To address this discrepancy between trial findings and limitations in the current field, we conducted a retrospective review of patients undergoing PSG. Our primary hypothesis was that nocturnal hypoxemia quantified during PSG is associated with an increased risk of ACS in pediatric populations with SCD. We also explored the hypothesis that nocturnal hypoxemia can be incorporated into association models for ACS in children with SCD to introduce preventive strategies to those at highest risk of this deadly complication.[17]

METHODS

A retrospective chart review of children ages 0 to 18 followed for SCD with a sleep study available at Children's of Alabama was performed. The SCD database at Children's of Alabama was cross-referenced with the sleep studies software database for the period of 2012 to 2018 to identify patients with SCD who had completed PSG. When more than one diagnostic sleep study was available for a specific child, we selected the results from the first PSG to avoid the effect of any intervention after the sleep study, such as surgeries and O_2 therapy, on the association. In 15 patients, the first available sleep study occurred after airway surgery for lymphoid tissue removal (tonsillectomy, adenoidectomy, or both) and were incorporated in this analysis. All data were abstracted by a board-certified sleep medicine physician who reviewed individual reports generated by the polysomnogram software to abstract the different sleep parameters, including the following: mean nocturnal oxygen saturation (SpO_2), percentage of total sleep time with $SpO_2 < 90\%$ (pTST $SpO_2 < 90\%$), apnea-hypopnea index (AHI), and percentage of total sleep time with end tidal CO_2 ($etCO_2$) > 50 mm Hg (pTST $etCO_2 > 50$). Clinical variables and outcomes associated with ACS were obtained from the SCD database (age, sex, race, phenotype, previous diagnosis of asthma, history of chronic hydroxyurea use, and chronic transfusion therapy). University of Alabama at Birmingham institutional review board approval was obtained before data collection and analysis.

Sickle cell database

This cohort comprised 859 children, aged 0 to 18 years, with confirmed sickle cell anemia diagnosis followed at a pediatric outpatient sickle cell clinic housed within an urban, tertiary academic medical center in Birmingham, Alabama. Hemoglobinopathy fractionation profile confirmed SCD phenotypes. Each patient was deidentified and assigned a unique study identification code. All descriptive and outcome variables for each individual were gathered through an electronic medical record extraction and entered in Research Electronic Data Capture, a secure web-based data management software.

Acute chest syndrome and asthma definitions

All participants were followed from 2012 through 2018 for capture of ACS episodes. ACS was defined as a new radiodensity on chest x-ray, accompanied by temperature > 38°C, increased work of breathing, or oxygen desaturation. Pneumonia diagnoses were also categorized as ACS. Both ACS and pneumonia diagnoses were captured through discharge records in the electronic medical record. Hospital admissions for pain that progressed to ACS or pneumonia were also counted as an ACS episode. Study participants were categorized as having asthma if they had a documented International Statistical Classification of Diseases and Related Health Problems, 10th ed. code in their problem lists for asthma or active asthma medications in the electronic medical record prescription database.

Polysomnography

All sleep studies were performed at Children's of Alabama and consisted of full 12-channel, in laboratory PSG, including the following: monitoring of electroencephalography, eye movements, chin electromyography, limb electromyography, thoracic and abdominal respiratory effort, airflow, electrocardiogram, snore sensor, and continuous pulse oximetry (using Nonin Xpod oximeter, Nonin Medical, Inc., Plymouth, Minnesota). PSG data collection and scoring were based on standardized protocols in accordance with the American Academy of Sleep Medicine guidelines.[18] Throughout the years the protocols have been adjusted to remain updated with newest guidelines. Children's of Alabama Sleep Center Lab has maintained uninterrupted accreditation through the American Academy of Sleep Medicine.

Statistical analysis

We performed descriptive analyses (means, standard deviations [SD]), medians, interquartile ranges, and frequency distributions (%) as appropriate to assess and describe the study participants. We conducted Chi-square, Fisher's exact, Mann-Whitney U,

Table 1—Baseline characters of the study population and further categorized by their ACS status.

Characteristics	No PSG (n = 749)	PSG (n = 110)	*P* Value	PSG with ACS (n = 59)	PSG with no ACS (n = 51)	*P* Value
Age at PSG, y, mean (SD)	N/A	9.45 (4.3)	—	10.62 (4.22)	8.11 (4.09)	<.01
Male, n (%)	394 (53)	56 (51)	.71	33 (56)	23 (45)	.26
Black or African American, n (%)	740 (99.1)	110 (100)	.60	59 (100)	51 (100)	1
Phenotype, n (%)			.0001			<.001
SS	370 (49.3)	81 (73.6)		51 (86.4)	30 (58.8)	
SB0	31 (4.1)	4 (3.6)		3 (5.1)	1 (2)	
SB+	90 (12)	9 (8.2)		0 (0)	9 (17.6)	
SC	230 (30.7)	16 (14.6)		5 (8.5)	11 (21.6)	
History of asthma, n (%)	244 (32.5)	68 (62)	<.0001	48 (81)	20 (39)	<.0001
History of ACS, n (%)	244 (32.5)	59 (53.6)	<.0001	59 (100)	—	—
History of multiple ACS, n (%)	118 (15.7)	40 (36.3)	<.0001	40 (68)	—	—
Hydroxyurea treatment, n (%)	305 (40.8)	72 (65.5)	<.0001	50 (85)	22 (43)	<.0001
Chronic transfusion treatment, n (%)	102 (13.6)	41 (37)	<.0001	25 (42)	16 (31)	<.05
Height, mean (SD)	135 (33.7)	138.7 (22.0)	.13	143.7 (20.4)	132.7 (22.43)	<.01
Weight, mean (SD)	40.7 (24.6)	41.6 (23.6)	.70	45.3 (23.0)	37.3 (23.8)	.08
BMI, mean (SD)	20.1 (5.2)	20.2 (6.2)	.95	20.6 (6.2)	19.7 (6.1)	.42
Hb level closest to PSG, mean (SD)	N/A	8.9 (2.2)	—	8.3 (1.3)	9.7 (1.7)	<.0001

ACS = acute chest syndrome, BMI = body mass index, Hb = hemoglobin, N/A = not available, PSG = polysomnogram, SD, standard deviation.

Student's *t* or Kruskal-Wallis tests as appropriate for initial univariate primary and secondary outcomes analyses. We performed logistic regression to evaluate the potential association between hypoxemia (mean nocturnal SpO_2 and pTST $SpO_2 < 90\%$) with the occurrence of ACS episodes, where ACS episodes serve as the dichotomous outcome. As a secondary analysis, logistic regression was also performed to compare those with history of single ACS episode vs those with multiple episodes of ACS regarding mean nocturnal O_2 saturation and pTST $SpO_2 < 90\%$. Multivariate logistic regression analysis was performed to verify the effects of other covariates (age, hemoglobin level, phenotype, hydroxyurea treatment, chronic blood transfusion, and asthma) on the occurrence of ACS in the presence of nocturnal hypoxemia. To quantify the effects of association, we estimated odds ratio with their 95% confidence intervals. All hypothesis tests were two-tailed, and we used a $P < .05$ to indicate statistical significance. We performed analyses in SAS for windows version 9.4 (Cary, North Carolina).

RESULTS

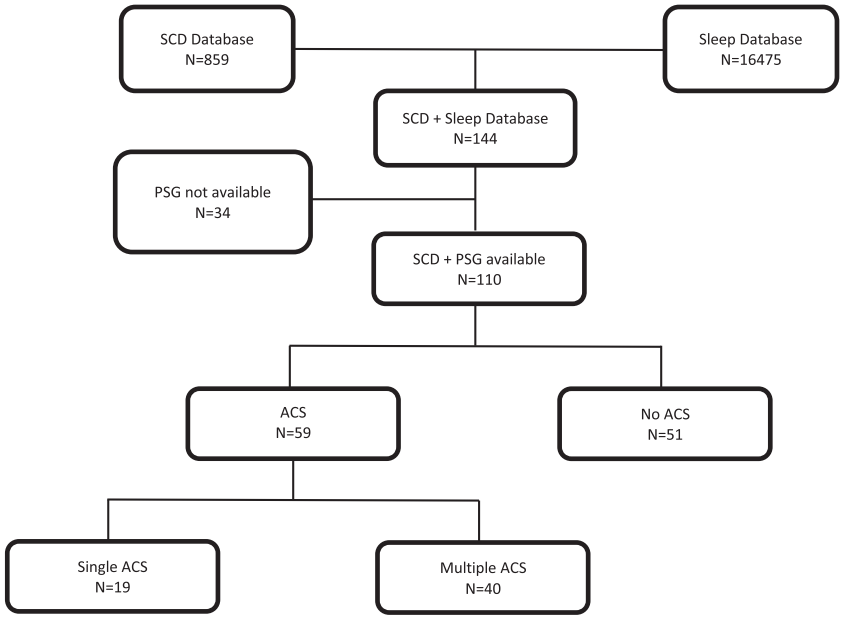
Recruitment and baseline characteristics

Cross-reference of the sleep center (16,475 studies) and sickle cell (859 patients) databases during the study period yielded 144 patients; 110 sickle cell patients successfully completed their sleep study. These patients had a higher rate of comorbid asthma, ACS events, hydroxyurea use, and chronic transfusion therapy compared with those who did not undergo PSG testing (**Table 1**). The four most common indications for PSG were obstructive sleep apnea (68 patients), snoring (50 patients), excessive daytime sleepiness (8 patients), and hypoxemia/oxygen requirement (7 patients). Some patients had more than one indication for the study and three did not have a listed indication. In 15 patients, the first available sleep study occurred after airway surgery for lymphoid tissue removal (tonsillectomy, adenoidectomy, or both), and these studies were incorporated in this analysis. Oxygen therapy was not instituted before the PSG for the studied cohort.

In reviewing the results of these 110 PSG studies, $etCO_2$ measurement was not available in seven sleep studies, mean oxygen saturation was not available in one study, and pTST $SpO_2 < 90\%$ was not available in three studies. Fifty-one of the 110 individuals had no prior history of ACS. Among the 59 (54%) patients who experienced at least one episode of ACS, 40 (68%) had multiple ACS episodes (**Figure 1**). The mean age at the time of the initial sleep study was 9.4 years (range: 14 months to 18 years). The average age at the time of first ACS attack was 4.1 years (range: 6 months to 16 years); therefore, the average time lapse between the ACS and first PSG was 5.3 years. Fifty-one percent of patients were males, 100% were African American, and 73.6% were homozygous for Hemoglobin SS (HbSS). Sixty-two percent of patients had a history of asthma (**Table 1**).

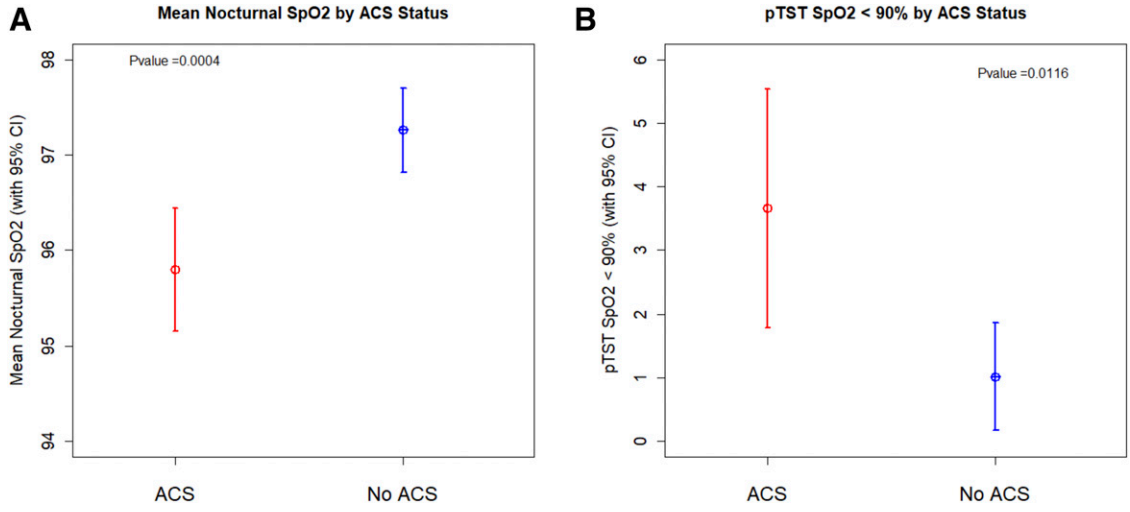
Compared with patients with no prior ACS, children with prior ACS were older (10.6 ± 4.2 vs 8.1 ± 4 years; $P < .01$) and taller (143.7 ± 20.4 vs 132.7 ± 22.4 cm; $P < .01$) at the time of sleep study; however, there was no difference in weight ($P = 0.08$) and body mass index ($P = .42$). Also, the ACS group was more likely to be homozygous for HbSS (86.4% vs 58.8%; $P < .001$), prescribed hydroxyurea (85% vs 43%; $P < 0.0001$), or chronic blood transfusion therapy (42% vs 31%; $P < 0.05$). Children with ACS were also more likely to have lower hemoglobin level close to the time of their PSG (8.3 ± 1.3 vs 9.7 ± 1.7 g/dl; $P < .0001$) (**Table 1**).

Figure 1—Flow chart of study population.



ACS = acute chest syndrome, PSG = polysomnogram, SCD = sickle cell disease.

Figure 2—Distribution of O_2 status during sleep study.



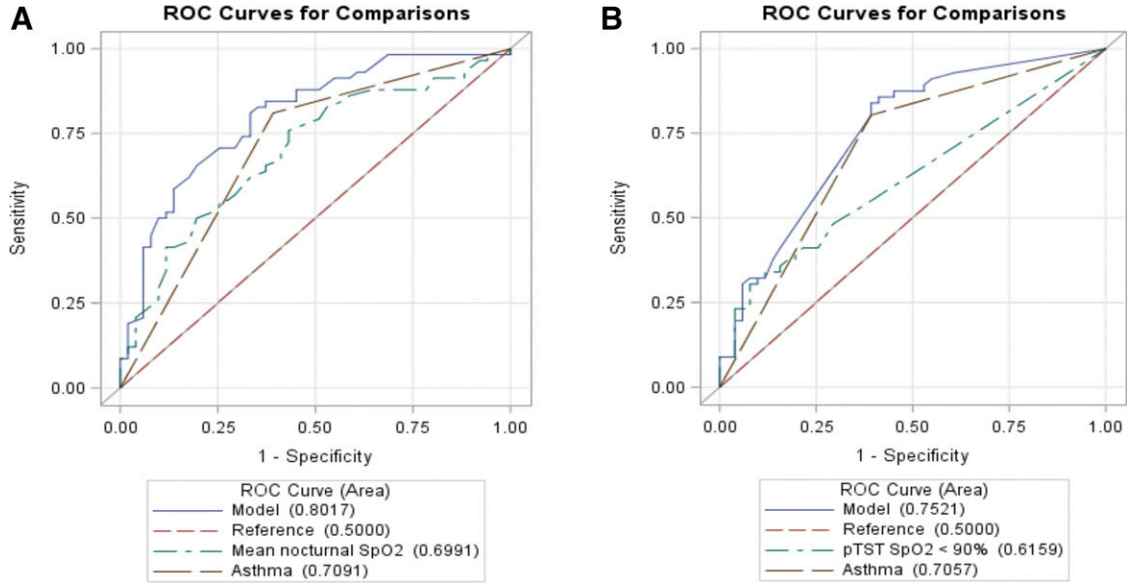
(A) mean O_2 saturation and **(B)** pTST SpO_2 < 90% measured during sleep study as a function of ACS status: N) patients with no ACS and Y) patients with ACS. ACS = acute chest syndrome, pTST SpO_2 < 90% = total sleep time with O_2 saturation below 90%.

Mean nocturnal SpO_2 and percentage of total sleep time with oxygen saturation < 90% (pTST SpO_2 < 90%) are associated with ACS

Univariate analysis showed that mean nocturnal O_2 saturation (SD) measured during PSG was lower in patients with ACS compared with those with no ACS (95.8% ± 2.4 vs 97.3% ± 1.6; $P < .0005$) (Figure 2A). Similarly, the mean pTST SpO_2 < 90% (SD) was significantly higher in the ACS group than the non-ACS group (3.7% ± 6.7 vs 1.0% ± 3.0; $P < .05$) (Figure 2B). Both mean nocturnal O_2 saturation and pTST SpO_2 < 90% were associated with ACS resulting in area under the curve (AUC) of the receiver operator characteristic (ROC) of .70 and .62 successively ($P < .001$). Asthma was also associated with ACS (AUC = 0.71, $P < .001$). Adding asthma to the model improved the AUC for both mean nocturnal O_2 saturation and pTST SpO_2 < 90% to .80 and .75 (Figure 3). Mean nocturnal O_2 saturation remained associated with ACS after adjustment for Asthma (AUC = .80, $P < .001$; increment of AUC = .09, $P = .001$).

Accordingly, using a mean nocturnal O_2 saturation cutoff value of 97.3%, we were able to distinguish between those with ACS vs those with no ACS with sensitivity of 76% and specificity of 57 with an AUC-ROC curve of 0.70. Also, with a cut-point of 2.7% for the pTST SpO_2 < 90%, we were able to distinguish between those with ACS vs non-ACS with specificity of 92%

Figure 3—Receiver operating characteristic curve for the association of hypoxemia and ACS.



ACS probability based on **(A)** mean nocturnal O_2 saturation: reference curve (0.50, red), mean SpO_2 (0.70, green), asthma (0.71, brown), and combined mean SpO_2 and asthma model (0.80, blue). **(B)** pTST SpO_2 < 90%: reference curve (0.50, red), pTST SpO_2 < 90% (0.62, green), asthma (0.71, brown), and combined pTST SpO_2 < 90% and asthma model (0.75, blue). ACS = acute chest syndrome, pTST SpO_2 < 90% = total sleep time with O_2 saturation below 90%.

and sensitivity of 30%, corresponding to an AUC-ROC curve of .62 (**Figure 3B**).

Asthma, age, and hemoglobin level are also associated with ACS

In multivariate logistic regression analysis, after adjusting for age, hemoglobin level, and phenotype, asthma remained independently associated with ACS (odds ratio: 7.5, 95% CI: 2.7, 20.7; $P < 0.01$). Age was also independently and positively associated with ACS (OR 1.15; $P < .005$). Hemoglobin level closest to the sleep study was negatively associated with the risk of developing ACS (odds ratio: 0.57; $P < .0001$) (**Table 2**).

Table 2—Multivariate analysis for the association of multiple covariates with ACS.

	Estimated Odds Ratio with 95% CI	*P* Value
Age (for 1-y increase)	1.17 (1.04, 1.33)	<.01
Hemoglobin level (for 1-unit increase)	0.57 (.40,0.82)	<.005
Sickle phenotype, SS vs not SS	1.83 (.55, 6.18)	.3275
Asthma, yes vs n/o	7.52 (2.73, 20.67)	<.0001

ACS = acute chest syndrome, CI = confidence interval.

No difference in nocturnal hypoxemia between those with single vs multiple ACS episodes

When looking at the secondary analysis regarding those with a history of single vs multiple ACS events, no significant difference was noted regarding mean nocturnal saturation ($P = .49$) and pTST SpO_2 < 90% ($P = .94$).

Other sleep variables were not associated with ACS

No significant relationship was noted between ACS episodes and other sleep variables such as AHI ($P = .62$), pTST $etCO_2$ > 50 ($P = .44$), nadir O_2 saturation ($P = .22$), arousal index ($P = .57$), and sleep architecture (**Table 3**).

DISCUSSION

The present study shows that comorbid nocturnal hypoxemia (measured during PSG with either mean nocturnal O_2 saturation or pTST SpO_2 < 90%) in children with SCD is associated with a history of ACS events. To our knowledge, this is the first study to show an association between nocturnal hypoxemia measured during overnight PSG and a history of ACS in children with SCD. The results are particularly credible given the large sample size, as well as findings consistent with previous studies showing asthma as a risk factor for ACS.[19] Moreover, the present study suggests nocturnal hypoxemia as a potentially modifiable risk factor for the development of ACS.

The prevalence of asthma (68%) and ACS (54%) in the patients referred for PSG evaluation was significantly greater compared with the entire SCD cohort (30% and 34%, respectively), as well as other historical SCD cohorts.[20,21] SCD phenotype, prevalence of multiple ACS, hydroxyurea use, and chronic transfusion therapy were also significantly different (**Table 1**). Such differences indicate selection bias, as patients referred for PSG are more likely to have underlying pulmonary morbidities and more severe SCD phenotype. The lack of diversity of our patients—all are African Americans—is representative of the population of patients with SCD in the Southeastern region

Table 3—Sleep parameters for ACS group vs no ACS group.

Sleep Variables	ACS (n = 59)	No ACS (n = 51)	*P* Value
Sleep efficiency	87.0 (8.2)	86.4 (13.9)	.79
TST, mean (SD) minutes	443 (49.65)	435.3 (57.31)	.46
% N1 sleep, mean (SD)	5.7 (4.2)	5.0 (3.7)	.34
% N2 sleep, mean (SD)	54.0 (7.9)	52.9 (10.25)	.52
% N3 sleep, mean (SD)	22.9 (7.3)	24.7 (8.2)	.25
% REM sleep, mean (SD)	17.2 (6.3)	17.4 (6.3)	.91
AHI ≥ 1, n (%)	25 (42%)	25 (49%)	.49
AHI ≥ 5, n (%)	10 (17%)	11 (22%)	.54
AHI, mean (SD)	2.66 (5.22)	4.92 (11.56)	.20
REM AHI, mean (SD)	9.28 (22.08)	10.86 (18.10)	.67
Central apnea index, mean (SD)	0.19 (0.23)	0.28 (0.60)	.30
OAHI, mean (SD)	2.46 (5.18)	4.63 (11.18)	.21
Nocturnal O_2 saturation, mean (SD)	95.8% (2.4)	97.3% (1.6)	<.0005
pTST SpO_2 < 90%, mean (SD)	3.7% (6.7)	1.0% (3.0)	<.05
Nadir O_2 sat %, mean (SD)	87.6 (5.8)	88.8 (5.7)	.27
% TST $EtCO_2$ > 50 (SD)	0.94 (5.06)	0.6 (3.26)	.67
Arousal index, mean (SD)	4.7 (3.9)	5.9 (6.7)	.29

ACS = acute chest syndrome, AHI = apnea-hypopnea index, $EtCO_2$ = end tidal CO_2, REM = rapid eye movement, SD = standard deviation, TST = total sleep time.

of the country. The higher proportion of patients on hydroxyurea and chronic blood transfusion among the ACS group is likely a reflection of the disease severity.

Children with lower nocturnal oxygenation, whether measured with mean nocturnal SpO_2 or pTST SpO_2 < 90% during PSG, had a higher prevalence of ACS. Such an association is not previously reported. In previous studies, daytime or nocturnal oxygen desaturation did not predict the risk for ACS in children.[11,22] Although the incidence of ACS is greater in younger children, 2 to 4 years of age, the prevalence is higher in older patients, as they are more likely to have a history of ACS. ACS patients being taller may be explained by the age difference given the similar body mass index between the two groups. The association of ACS with asthma is previously documented.[6] Most previous studies revealed an increased risk of ACS with higher steady hemoglobin level.[12,23] The lower level of hemoglobin in our ACS group—even after correcting for other covariates—may reflect more severe disease at steady state with hyperhaemolysis predisposing patients to ACS when they are exposed to triggering factors or it may reflect a referral bias to PSG, given the erroneously lower reported oxygen saturation with SCD.

As more sleep studies are performed for patients with SCD (17% of our SCD patients had a sleep study), clinicians need guidance as to how to interpret and use these data. To our knowledge, this study is the first to suggest specific values of nighttime oxygenation that are associated with increased occurrence of ACS in this specific population. These data could help develop more individualized management for pediatric SCD. We identified two different ACS risk determinants in children with SCD undergoing PSG. One is the mean nocturnal SpO_2 of < 97.3%, which could be used as a screening tool, given its reasonably high sensitivity of 76%; however, the overlap with the normal range and low specificity make it less practical in a clinical setting. The other risk determinant, pTST SpO_2 < 90% of greater than 2.7%, has a clearer clinical indication as a confirming indicator with a high specificity of 92%. Together with the results of future prospective studies, mean nocturnal SpO_2 and pTST SpO_2 < 90% can be used to guide inclusion criteria for future trials, inclusive of treatment trials, such as one examining supplemental oxygen during sleep in SCD. Asthma is the covariate most strongly associated with ACS, and this study demonstrated that adding asthma to the model further improved the accuracy of association with ACS admissions. These results suggest an important association of nocturnal hypoxemia and ACS. Depending on the temporal relationship, nocturnal hypoxemia can be either a modifiable predisposing factor or a consequence of ACS. In addition to helping clinicians and researchers interpret sleep studies in SCD patients, nocturnal oxygen parameters could help select patients with SCD for supplemental oxygen trials to decrease ACS occurrence.

Given that all sleep studies for our participants were performed after the onset of ACS, the nocturnal hypoxemia detected can be either a predisposing factor or a consequence of the ACS. To investigate this further, we propose that if nocturnal hypoxemia is a sequela of lung injury from the ACS, patients with recurrent episodes would have a cumulative effect and, consequently, worse nocturnal hypoxemia. Given that there was no difference in the levels of nocturnal hypoxemia between those with single vs multiple ACS episodes, we presume that nocturnal hypoxemia may be a predisposing factor for the development of ACS. Given the small sample size, however, a difference in nocturnal saturation between those with single vs multiple ACS events could have been missed. Moreover, a greater

lung injury may have been caused by the first episode of ACS at a younger age—a period of fast lung growth—with a lesser impact of the subsequent ACS events. Nevertheless, the intrinsic limitations of a retrospective study do not allow for any conclusive assumptions regarding temporal association between nocturnal hypoxemia and ACS. Therefore, the opinion that nocturnal hypoxemia may be a predisposing factor for the development of ACS is purely speculative, and future prospective studies are needed to address this issue adequately.

Although obstructive sleep apnea pathophysiology is thought to potentiate the pathways leading to predisposition of patients with SCD to ACS, there is no evidence to support such a theory[11]; similarly, our results did not show an association between AHI and ACS events. According to the Haldane effect, carbon dioxide can reduce the affinity of the hemoglobin to oxygen. Theoretically, higher CO_2 therefore may reduce the ability of HbSS to carry O_2, further compromising tissue hypoxia. In adults, carbon dioxide measured with arterial blood gas did not differ between ACS and non-ACS groups.[24] Similarly, our data confirm that hypercapnia measured overnight in children with SCD was not associated with ACS.

The current study shows that two different nighttime hypoxemia parameters measured with the gold standard PSG are associated with a history of ACS in children with SCD. Interpretation of the present study's results should consider its limitations as a retrospective study in which all PSGs were performed after ACS occurrence. In addition, the potential selection bias of clinical severity for patients referred for PSG cannot be understated.

These results emphasize the great need for prospective cohort studies starting at a young age before the development of any ACS episode, in line with the most recent SCD guidelines by the American Society of Hematology.[4] Ideally, patients would be screened early in life, before the age of peak ACS events, at 2 to 4 years of age. The findings also call for clinical trials of supplemental oxygen during sleep for patients with SCD with mean nocturnal $SpO_2 < 97.3\%$ and pTST $SpO_2 < 90\%$ greater than 2.7% of the night as such patients have a high probability of developing ACS. Positive results of such trials may call for sleep-study screening of patients with SCD to intervene early with the goal of preserving organ function or at least delaying organ injury.

ABBREVIATIONS

ACS, acute chest syndrome
AHI, apnea-hypopnea index
PSG, polysomnography
SCD, sickle cell disease
SDB, sleep-disordered breathing
SpO_2, mean nocturnal oxygen saturation

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All authors have seen and approved the manuscript as submitted. We warrant that the article is the authors' original work, that the article has not received prior publication and is not under consideration for publication elsewhere. On behalf of all the authors, the corresponding author shall bear full responsibility for the submission. This research has not been submitted for publication, nor has it been published in whole or in part elsewhere. All authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *Journal of Clinical Sleep Medicine*. The work for this study was performed at the University of Alabama at Birmingham. None of the authors has any conflicts of interest to disclose. No financial support was provided for development of this study.