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Sleep disordered breathing does not predict acute severe pain episodes in children with sickle cell anemia

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Abstract

Conflicting evidence has suggested that low mean nocturnal hemoglobin oxygen saturation (SpO₂) predicts future hospital days for acute severe pain in children with sickle cell anemia (SCA). In an unselected multi-center prospective cohort study, we tested the hypothesis that either low mean nocturnal SpO₂ or high obstructive apnea-hypopnea index (OAH; the number of obstructive apneas and hypopneas with $\geq 3\%$ desaturation or arousal per hour of sleep) or high oxygen desaturation index (ODI; number of $\geq 3\%$ desaturation from baseline saturation per hour of sleep) is associated with increased incidence rates of pain. A total of 140 children with SCA with a median age of 10.8 years (interquartile range 7.2) were followed for a median 4.9 years (interquartile range 1.8). Overnight polysomnography evaluations at baseline health were measured and adjudicated centrally. Multivariable models created in two steps were included. First all plausible covariates were included in a screening model. Subsequently, covariates meeting significance criteria of $p < 0.20$ were included in the final model. Contrary to our hypothesis, higher (but not lower) mean nocturnal SpO₂ was associated with higher rates of pain episodes (IRR 1.10, 95% CI [1.03-1.18], $p = 0.004$). Higher log OAH did not pass screening criteria. Higher log ODI was not significantly associated with higher rates of pain episodes (IRR 0.93, 95% CI [0.82-1.06], $p = 0.28$). Neither low nocturnal SpO₂, higher OAH, nor higher ODI were associated with clinically relevant increased incidence rates of acute severe pain episodes.

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Authorship Contributions: Drs. Willen and DeBaun had full access to all of the data in the study and take responsibility for the integrity of the data, the accuracy of the data analysis, and the work as a whole. Dr. Willen interpreted the data, created the initial draft, and finalized the manuscript for submission; Dr. Rodeghier developed the statistical approach, performed those analyses, reviewed the integrity of those analyses, and reviewed and revised the manuscript; Dr. Rosen contributed to the development of the SAC project, study concepts and procedures, and reviewed and helped revise the manuscript; Dr. DeBaun served as the principal investigator for the SAC project, design the concepts for SAC and this manuscript, interpreted the results, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

The authors have no conflicts of interest to disclose.

Introduction

Sickle cell anemia (SCA) is the most common inherited blood disorder in the United States, and the burden is continuing to increase worldwide.¹ The two most common complications of SCA requiring hospitalization are acute vaso-occlusive pain (referred to as pain) and acute chest syndrome (ACS) episodes. One potential risk factor for sickle cell disease (SCD) related morbidity is hemoglobin oxygen desaturation, which leads to hemoglobin polymerization, sickling of erythrocytes, and increased red blood cell adherence to the endothelium, ultimately resulting in vaso-occlusion and tissue hypoxia.^{2,3}

Previous studies have investigated the relationship between hemoglobin oxygen saturation, as measured by pulse oximetry (SpO₂), and SCA-related morbidity with conflicting results. In a prospective cohort of 130 children with SCA, there was no association between lower mean daytime SpO₂ obtained at baseline health exam and incidence rates of pain or ACS.⁴ Similar findings were seen in a retrospective cohort of 183 children with SCA from the Dallas Newborn Cohort for incidence rates of ACS episodes.⁵ In a third study, a prospective single-center cohort of 39 consecutive children with homozygous SS or S/β₀ thalassemia, neither mean daytime nor mean nocturnal SpO₂ was associated with increased incidence rates of pain or ACS episodes.⁶

The prior three studies measuring mean SpO₂ levels (three daytime studies and one nighttime study) have not demonstrated any association between lower mean SpO₂ and increased incidence of pain or ACS in children with SCA. In contrast, only one study has demonstrated a positive association. A single site prospective study by Hargrave et al. demonstrated that low mean nocturnal SpO₂, based on overnight pulse oximetry measured either at home or in-patient, was associated with an increased number of hospital days for pain episodes.⁷ Conflicting results describing the relationship between low mean nocturnal SpO₂ measurements and SCA morbidity (pain and ACS episodes) has resulted in ambiguity as to whether children with low mean nocturnal SpO₂ should be prescribed supplemental oxygen at night to prevent SCA related morbidity.

The National Heart Lung and Blood Institute funded our multi-disciplinary research team of pediatric hematologists, pulmonologists, and sleep experts to address whether mean nocturnal SpO₂ predicted future pain episodes requiring hospitalization. We created a multi-center prospective cohort of unselected children with SCA that received a full 12-channel polysomnography (PSG). In this cohort, we tested the primary hypothesis that low mean nocturnal SpO₂ is associated with increased incidence rates of pain episodes in children with SCA. We also tested the hypothesis that obstructive sleep apnea syndrome (OSAS), as defined by high obstructive apnea-hypopnea index (OAH) or by high oxygen desaturation index (ODI), is associated with an increased incidence of pain episodes in children with SCA. Finally, we explored whether there is any relationship between mean nocturnal SpO₂, OAH, and ODI and increased incidence of ACS episodes in children with SCA.

Methods

A prospective cohort study of children and adolescents from the Sleep and Asthma Cohort (SAC) was assembled. Children with SCA, defined as homozygous for sickle cell hemoglobin [HbSS ($N=240$)] or compound heterozygous for sickle β zero thalassemia [HbS β^0 ($N=12$)], ranging from 4 to 18 years of age were enrolled at three clinical SCA centers: Washington University School of Medicine in St. Louis, Missouri; Case Western Reserve University in Cleveland, Ohio; and University College London in London, UK (which recruited from three London hospitals) between 2005 and 2011. Institutional review boards for each US site approved the study protocol. Ethical approval was provided by the National Research Ethics Service which allowed for recruitment from all 3 UK sites. All study participants were unselected for respiratory disease and prospectively observed for at least 3 years. Children were not eligible for participation in the study if they received long-term blood transfusion therapy due to the known impact of transfusion therapy on pain episodes.⁸ Participants were also not eligible if they received long-term continuous positive airway pressure support, had chronic lung disease other than asthma, smoked cigarettes, or were known to be human immune deficiency virus (HIV)-positive due to the known association between HIV-positivity and chronic lung disease in children and adolescents.⁹ If patients were initiated on regular blood transfusion therapy during the study period, they were retained in the cohort and a separate analysis was performed including these participants. Parents provided written informed consent for all participants and patients provided assent when appropriate. Laboratory testing, daytime SpO₂, and polysomnography were performed at study entry when patients were at baseline health. Study visits were in coordination with routine clinical care and participants were followed every three to six months.

Definition of vaso-occlusive episodes: acute pain and acute chest syndrome

An acute pain episode was defined as a SCA-associated pain episode requiring admission to the hospital and treatment with opioids. Emergency department visits were not included in this definition due to the variation in outpatient pain management practices and to capture only acute severe pain events. Headaches treated with opioids were also not included in this definition due to the difference in proposed pathophysiology of headaches as opposed to acute vaso-occlusive pain.¹⁰ To replicate the Hargrave et al. analysis, hospital days for pain rate (defined as hospital days of pain per years of follow-up) was also examined. ACS was defined as at least one new radiodensity on radiograph of the chest in addition to at least one of the following: temperature greater than 38.5°C, decreased SpO₂ from baseline, or increased respiratory rate.^{11,12} A new diagnosis of pneumonia was considered an ACS episode. The principal investigator (MRD) visited each site and reviewed all pain and ACS episodes during the first three years of the cohort to ensure a uniform definition of pain and ACS at each site in this multi-center study.

Definition of Obstructive Sleep Apnea Syndrome (OSAS), Obstructive Apnea-Hypopnea Index (OAH), and Oxygen Desaturation Index (ODI)

OAH and ODI were calculated based on the American Academy of Sleep Medicine pediatric criteria.¹³ Respiratory event types (obstructive, mixed, hypopneas, central) were

summarized as indices (the number of respiratory events divided by the hours of total sleep time). The OAHl was then defined as the sum of all obstructive and mixed apneas, plus hypopneas associated with a 50% reduction in airflow and either at least 3% desaturation or electroencephalographic arousal, divided by hours of total sleep time. The ODI was defined as the number of at least 3% desaturation from baseline saturation per hour of sleep.

Polysomnography

At each study site, SAC study-certified technicians performed overnight full 12-channel, in-laboratory research PSG including the following: monitoring of electroencephalography (EEG), eye movements (electro-oculogram; EOG), chin and limb electromyogram (EMG), thoracic and abdominal respiratory effort, airflow (thermistors and nasal pressure transducer), snore sensor, electrocardiography (ECG), and continuous measurements of nocturnal SpO₂ (using Masimo SET (v2), Irvine, CA). All data collection utilized standardized protocols according to the American Academy of Sleep Medicine guidelines for data acquisition and pediatric scoring.¹³ All PSGs were read centrally at Vanderbilt University School of Medicine.

Statistical analysis

Negative binomial regression was used to test the association between nocturnal SpO₂ and the incidence rates of pain and ACS episodes. Covariates in the primary models for pain and ACS episodes included: age at the time of the sleep study, gender, hemoglobin, white blood cell count (WBC), OAHl, and mean nocturnal SpO₂. The log value of OAHl and ODI was used for a continuous measure because the distributions were positively skewed. Multivariable models were constructed in two steps. First, all covariates were included in a screening model. Subsequently, those covariates meeting a significance criterion of $p < 0.20$ were included in the final model for pain or ACS episodes. The variance inflation factor (VIF) was used to assess multicollinearity using a threshold of 3.0. The highest VIF value was 1.6, indicating that collinearity is not a concern in these data. All tests for significance were two-tailed. P-values of < 0.05 were considered significant in the final models. Analyses were conducted using IBM SPSS Statistics (Version 23, Armonk, NY, IBM).

Results

Recruitment and baseline characteristics

Of the 252 participants with SCA who underwent PSG, 243 had complete data that were able to be scored according to the American Academy of Sleep Medicine guidelines.¹³ Of these, 223 participants had values for pain and ACS after PSG; missing data were due to lack of follow-up. Among the 223 participants, 18 participants were on hydroxyurea therapy at the time of PSG and one had a missing hydroxyurea status. These 19 participants were excluded from the primary analyses due to the known association between hydroxyurea and increased baseline SpO₂ measurements (hydroxyurea results in an increase in the percentage of fetal hemoglobin [HbF] and shifting of the oxygen dissociation curve to the left).¹⁴ After PSG was completed, 59 patients were started on hydroxyurea therapy, 6 were started on chronic blood transfusion therapy, and 1 participant was started on both therapies. These individuals were not included in the primary analysis (Figure 1). We did include the

participants that started hydroxyurea, regular blood transfusion therapy or both after polysomnography in a secondary analysis, and there was no appreciable difference in the results (See Online Supplement).

The final sample included 140 participants with a median age of 10.8 years (IQR 7.2). Participants were followed for a median of 4.9 years (IQR 1.8) after PSG, Table 1. The median (IQR) values were 96.4% (4.6) for mean nocturnal SpO₂ and 97.0% (4.9) for mean daytime SpO₂. Approximately 17% of our cohort (N=24) had a mean nocturnal SpO₂ less than 92% (Figure 2). Participants prescribed hydroxyurea, compared to those who were not prescribed hydroxyurea, were noted to have higher rates, not lower rates, of acute severe pain (mean 1.34 episodes/patient year versus 0.58 episodes/patient year; $p < 0.001$) and ACS (mean 0.33 versus 0.19; $p < 0.001$) episodes during the follow-up period.

Low nocturnal oxygen saturation is not associated with increased incidence rates of acute severe pain episodes or acute severe pain days

In the opposite direction of our hypothesis, after adjusting for age in the final model, higher, not lower, nocturnal SpO₂ was associated with increased incidence of pain episodes, such that each increase of 1% in SpO₂ was associated with a 10% increased rate of future pain episodes (incidence rate ratio (IRR) 1.10; 95% CI [1.03-1.18]; $p=0.004$), Table 2. Higher nocturnal SpO₂ was not associated with more pain days per year (IRR 1.09; 95% CI [1.00, 1.19]; $p=0.058$), again in the opposite direction of our hypothesis. The slope of the bivariate relationship between nocturnal SpO₂ and incidence of pain was positive (i.e., the higher the SpO₂, the higher the incidence of pain events), Figure 3. The positive slope means there is no clear-cut threshold (90%, 92%, 95%, etc.) below which mean nocturnal SpO₂ values will be associated with higher rates of pain events when compared to individuals above the threshold. No significant difference was seen in including or excluding participants receiving disease modifying therapy such as hydroxyurea or chronic blood transfusions. The analysis was repeated including the 59 participants started on hydroxyurea and the 6 participants started on chronic blood transfusion therapy (N=204). Higher nocturnal SpO₂ was again associated with an increased incidence rate of future pain episodes (IRR 1.11; 95% CI [1.06-1.17]; $p < 0.001$) (see Online Supplement).

Neither low nocturnal oxygen saturation, high OAHl, nor high ODI are associated with increased incidence rates of pain or acute chest syndrome

In the screening model used to evaluate the potential effect of OAHl on future rates of pain episodes, after adjusting for age, sex, WBC, hemoglobin, and mean nocturnal SpO₂, log OAHl did not pass the screening threshold ($p = 0.31$). In the final model evaluating the effect of ODI on future rates of pain episodes, ODI was not significant after adjusting for age ($p = 0.28$).

Mean nocturnal SpO₂ did not pass screening in the model to evaluate the effect of mean nocturnal SpO₂ on future ACS rates, after adjusting for age, sex, WBC, hemoglobin, and log OAHl (IRR 1.05; 95% CI [0.95-1.16]; $p = 0.37$). In the final model evaluating for the effect of log ODI on future ACS episode, ODI was not significant with the same set of covariates ($p = 0.74$).

Similar to our previous findings, no significant difference in the effect of SpO₂ on ACS rate was seen by including or excluding participants receiving disease modifying therapy such as hydroxyurea or chronic blood transfusions. The analysis was repeated including the 59 participants started on hydroxyurea and the 6 participants started on chronic blood transfusion therapy (N=204). No relationship was noted between mean nocturnal SpO₂ and incidence of ACS episodes (IRR 1.13; 95% CI [0.99-1.28]; $p = 0.06$) (see Online Supplement).

Low daytime oxygen saturation is not associated with increased incidence rates of acute severe pain or ACS

Higher mean daytime SpO₂ was also associated with increased incidence of pain episodes after adjusting for age in the final multivariable model (IRR 1.11; 95% CI [1.04-1.19]; $p = 0.001$). Higher mean daytime SpO₂ was not associated with ACS after adjusting for sex, age, WBC, hemoglobin, and log OAHl (IRR 1.09; 95% CI [0.98-1.20]; $p = 0.11$).

Discussion

When a child with SCA has a low nocturnal SpO₂ and a history of increased acute pain episodes, clinicians are without clear evidence that the use of supplemental oxygen will attenuate the incidence of future acute pain episodes. We conducted a prospective cohort study of children with SCA receiving rigorously performed sleep studies to determine if mean nocturnal SpO₂ was associated with either future pain or ACS episodes. Our results did not provide any evidence that low mean nocturnal SpO₂, high OAHl, or high ODI measurements were associated with increased incidence rates of pain or ACS episodes.

Despite having results contrary to our hypothesis, we believe our results are credible for the following reasons: 1) consistency of our findings with the two other prospective cohort studies demonstrating that mean daytime SpO₂ was not associated with increased incidence rates of pain^{4,6}; 2) the incidence rates of acute pain episodes requiring hospitalization of 0.80 events per patient year (including patients receiving disease modifying therapy, N= 204) was similar to two large cohorts of children with SCA, the SIT Trial (n=934) and the Cooperative Study of Sickle Cell Disease (n=349), 0.61 and 0.58 per patient year, respectively¹⁵; 3) rigorously obtained PSG evaluations with central adjudication in 140 children followed for 5 years coupled with the prevalence of sleep disordered breathing in this cohort being similar to the range of sleep characteristics in African-American children without SCA.¹⁶

Undoubtedly after completion of any study that did not confirm the primary hypothesis (and found a reverse association), there is some concern about spurious results and power of the study to test the hypothesis. However, these concerns are reduced for our study because we did find statistically significant results, with a moderate-sized coefficient, albeit in the opposite direction of the hypothesis (higher, not lower, SpO₂ measurements are associated with increased acute pain episodes). Second, in our cohort, similar to previous studies that did not find a relationship between low mean daytime SpO₂ and SCA related morbidity.^{4, 5, 6} In our study, for the primary hypothesis, the 95% confidence interval is narrow, describing the relationship between mean nocturnal SpO₂ oxygen measurements and pain episode

incidence rate (IRR 1.10; 95% CI [1.03-1.18]; $p = 0.004$). Additionally, OAHl and ODI are more refined approaches to determine sleep-disordered breathing than mean nocturnal SpO₂. We did not find any evidence that OAHl or ODI were associated with increased rates of pain. Our results demonstrate no clinically significant relationship between lower mean nocturnal SpO₂, OAHl or ODI, and future pain events in an unselected cohort of children with SCA, but instead a relationship between higher SpO₂ and increased incidence of pain events. We are unaware of the biological basis explaining why an increase in daytime or nocturnal SpO₂ would be associated with increased incidence rates of pain. Additional studies are needed to assess the biological basis, if any, of these findings.

Our prospective cohort study differed significantly from the only other prospective cohort of children with SCA to assess the influence of mean nocturnal SpO₂ oxygen measurements and its relationship to acute pain. Some of the key characteristics in the Hargrave et al. study which distinguish their study design from our study, include, but are not limited to: a single-center study which typically overestimates the effect size;¹⁷ the use of a pulse oximeter reading without the full benefit of polysomnography evaluation, which is considered the gold standard for assessment of nocturnal desaturations; and the primary analysis which did not correct for multicollinearity. Additionally, in our study we determined mean nocturnal SpO₂ measurement as part of an overnight PSG study using a Masimo pulse oximeter. An inherent challenge in using pulse oximetry measurements is the ability to differentiate true desaturation from motion artifact. A study of 20 pulse oximetry machines demonstrated that the Masimo SET R machine used in our cohort exhibited the best overall performance, with a sensitivity and specificity of 98% and 93%, respectively.¹⁸ In contrast, the Hargrave et al. analysis used Ohmeda Biox 3700, a machine with relatively poor test characteristics.¹⁹ Another major difference between our study and Hargrave et al. was the primary outcome measure. Our primary measure for severity was discrete events of acute vaso-occlusive pain, the standard strategy for assessment of pain in SCA therapeutic trials;^{20, 21} in comparison, Hargrave et al. elected to use the number of acute pain days in the hospital, an outcome that may be more variable based on family dynamics and physician preference. Table 3 summarizes the similarities and differences between the current study and Hargraves et al.

Despite the observation that an increase in OAHl was not associated with an increase in the incidence of ACS in our study, the direction of the association (higher OAHl is associated with higher incidence rate of ACS) is in agreement with our understanding of the pathophysiology of SCA. When including the cohort receiving disease modifying therapy, our results are just barely above the level of statistical significance, and do not exclude the possibility that higher OAHl correlates with higher risk for ACS. In this cohort, the median OAHl of 0.6 is in the range of normal,²² suggesting our population is similar to the general population of children without SCA. Thus, in a child with SCA that has recurrent ACS episodes and evidence of severe OSAS, specific interventions may be considered given the benefits in the general pediatric population.²³ However, a prospective cohort study would need to validate the potential benefits and risks of this intervention for decreasing SCA related morbidities or other morbidities.

Our study had several limitations. In our study, hydroxyurea was not associated with a decrease in the rates of pain and ACS during the study period, thus we elected to exclude

participants on hydroxyurea and started on chronic blood transfusion therapy after initial PSG. However, our results are generalizable to most children with SCA because despite a clear benefit of hydroxyurea therapy, almost a third of children with severe disease are not on hydroxyurea therapy.²⁴ Additionally, we performed a secondary analysis including those started on hydroxyurea or chronic blood transfusion therapy after their first sleep study and found no significant difference in our results. Completion of a sleep study provides numerous parameters to consider to evaluate the relationship between sleep disordered breathing and other characteristics. However, we focused our analysis on only three well established measurements of sleep disordered breathing (mean nocturnal SpO₂, ODI, and OAH). Increasing the number of sleep parameters that may predict acute severe pain or ACS episodes beyond our primary and secondary outcomes would undoubtedly increase the likelihood of false positive results and would be considered exploratory.

Our 5-year multi-center prospective cohort study demonstrates that in an unselected group of children with SCA, neither low mean nocturnal SpO₂ nor elevated ODI or OAH measures predict future pain or ACS events. Prior to starting nocturnal oxygen supplementation in children with decreased low mean nocturnal SpO₂ or elevated ODI or OAH measures with the intent of decreasing future SCD related morbidity, careful consideration should be undertaken to weigh the individual risks and benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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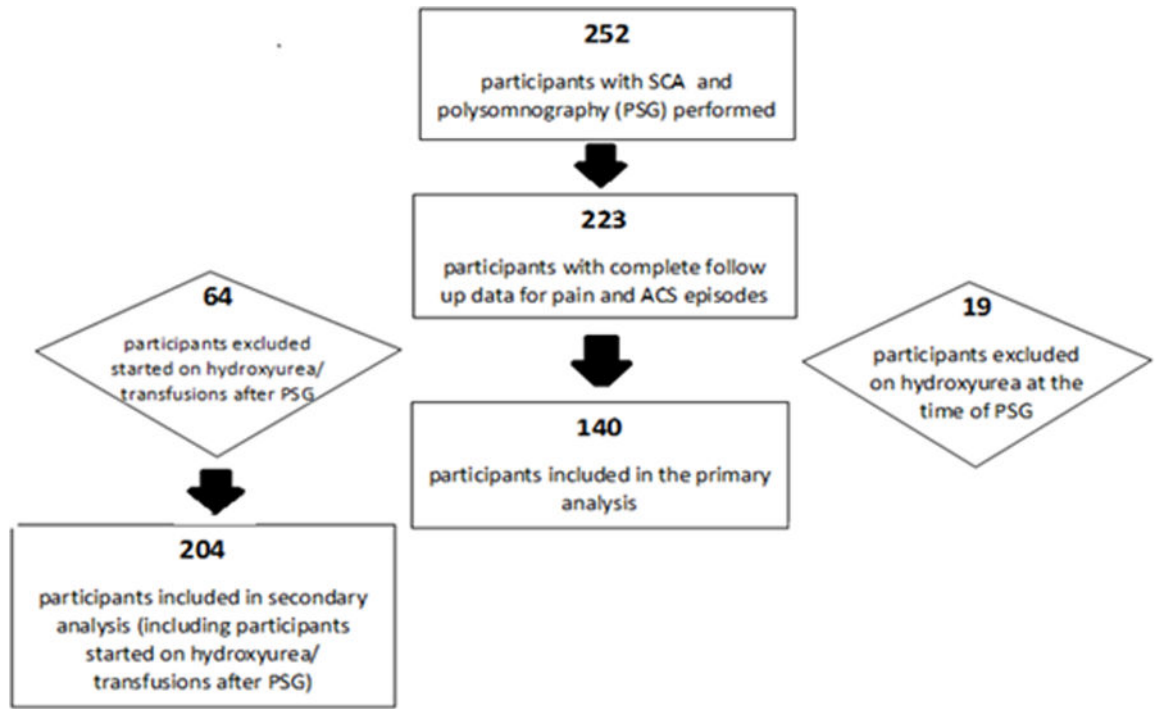


Figure 1.

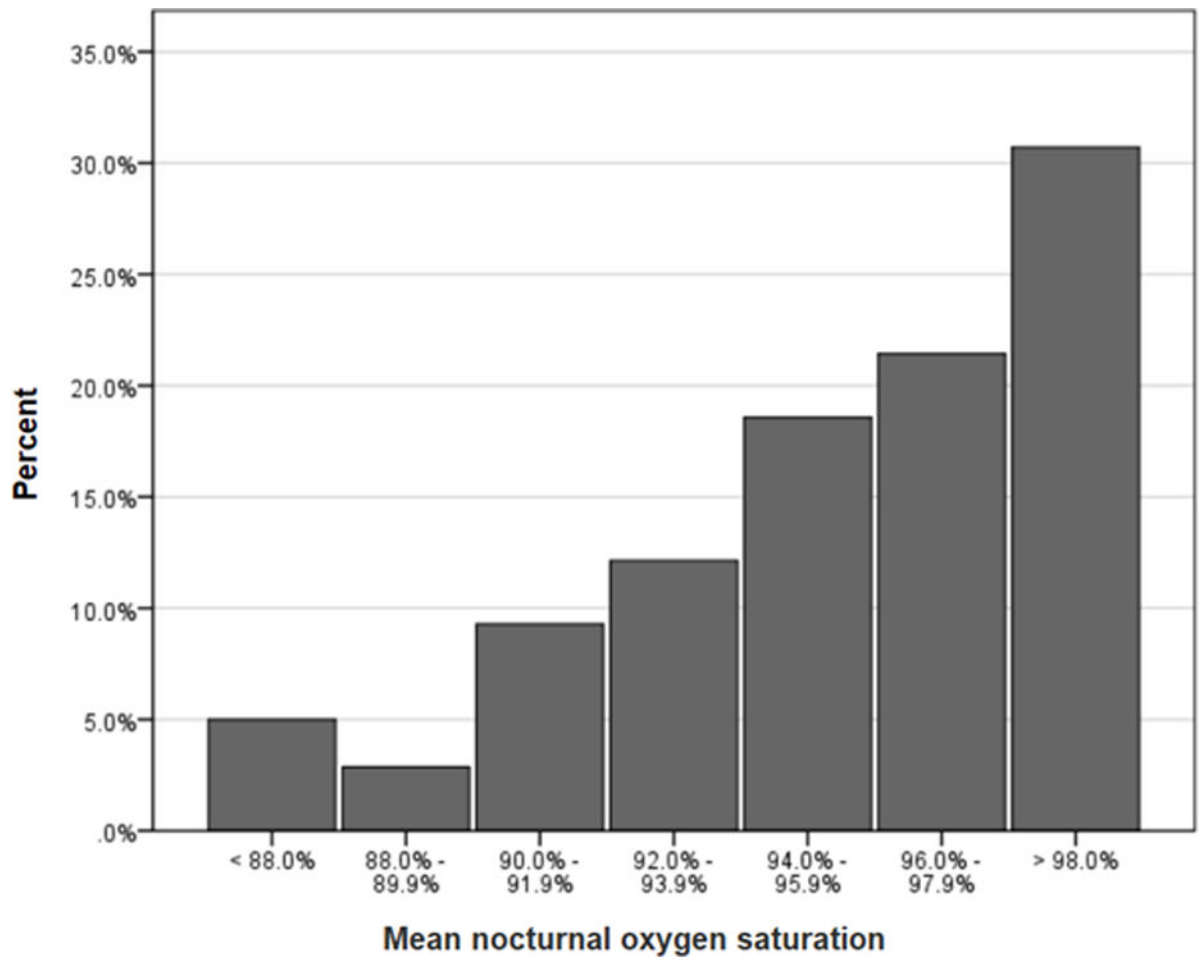


Figure 2.

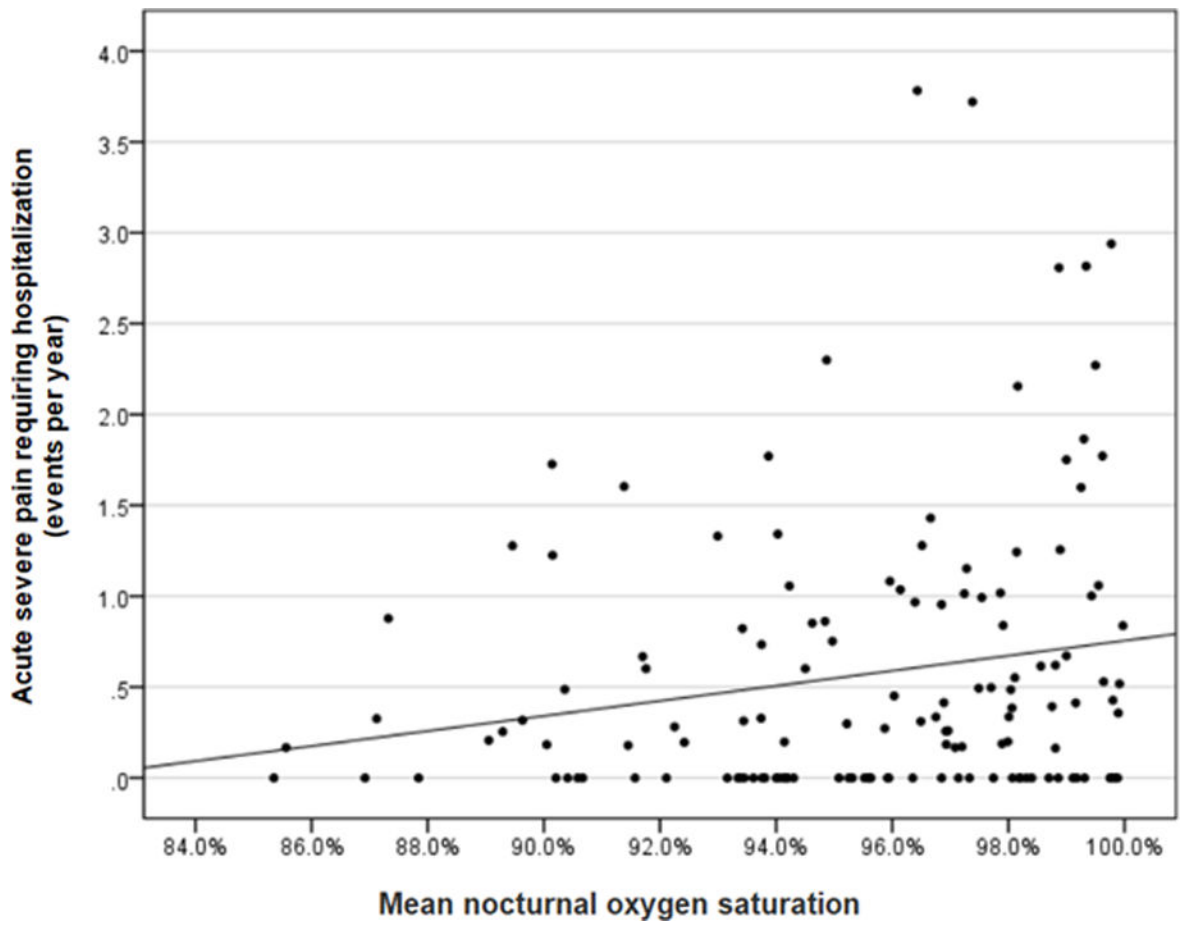


Figure 3.

Table 1

Characteristics of the Sleep and Asthma Cohort (SAC) study population ($N=140$) that completed both baseline polysomnography and were followed prospectively to assess acute vaso-occlusive pain events requiring hospitalization and acute chest syndrome events for a median of 5.0 years.

Characteristic	Summary statistics in cohort (n=140) [#]
Age at polysomnography, years	10.8 (7.2)
Male (%)	47.9
Total follow-up time after polysomnography (years)	4.9 (1.8)
Hemoglobin (g/dl)	8.1 (1.9)
White blood cell count ($\times 10^9/L$)	11.7 (3.9)
Reticulocytes (%), n=139	10.2 (6.9)
Daytime hemoglobin oxygen saturation (%), n=135	97.0 (4.9)
Obstructive apnea hypopnea index	0.6 (2.0)
Nocturnal hemoglobin oxygen saturation (%)	96.4 (4.6)
Oxygen desaturation index, 3%	2.2 (5.7)
Prospective rate of pain episodes per year, mean (std. dev.)	0.57 (0.76)
Prospective rate of ACS episodes per year, mean (std. dev.)	0.17 (0.29)

[#]Median and IQR are presented for variables, unless otherwise indicated.

Table 2

Final negative binomial regression models for prospective rates of vaso-occlusive pain or pain days per year^{**} with nocturnal oxygen saturation and obstructive apnea hyponea index (OAH) in children with sickle cell anemia ($N = 140$) from the Sleep and Asthma Cohort (SAC) study. The initial model included age at the time of the sleep study, gender, hemoglobin, white blood cell count (WBC), OAH, and mean nocturnal SpO₂. The log value of OAH was used for a continuous measure because the distribution was positively skewed

	IRR	95% CI	P-Value*
1. Prospective rates of pain events, final model			
Age at polysomnography	1.10	1.04-1.16	<0.001
Nocturnal oxygen saturation	1.10	1.03-1.18	0.004
2. Pain days per year, final model			
Age at polysomnography	1.12	1.05-1.21	0.001
Sex (male)	0.61	0.34-1.12	0.112
Nocturnal oxygen saturation	1.09	1.00-1.19	0.058

* Two-tailed

** Acute chest syndrome is not shown since no variable passed screening

Table 3

Similarities and differences between prior prospective cohort of children with mean nocturnal oxygen saturation demonstrating increased incidence of severe pain days⁷ and the current multi-Sleep and Asthma Cohort (SAC) study, demonstrating no increase incidence rates of acute pain episodes requiring hospitalization.

	Hargrave et al.	Sleep and Asthma Cohort (SAC)
Sample size	N = 95	N = 140
Number of institutions involved in the study	Single institution	Multi-institution (3 large pediatric centers)
Management of hydroxyurea	Excluded from all analyses	Excluded from all analyses
Definition of pain	Hospital treatment (emergency department visit or hospital admission)	Hospital admission only
Outcome measurement used	Hospital days for pain per years of follow-up	Incidence rate of hospitalization for acute pain per patient year
Measurement of oxygen saturation	Pulse oximetry at home (N = 63) or in laboratory (N = 27)	Full 12-channel, in-laboratory research polysomnography with central adjudication (N = 140)
Pulse oximetry machine used	Ohmeda Biox 3700	Masimo SET (v2)
Measurement modality	Pulse oximetry (SpO ₂)	Pulse oximetry (SpO ₂), oxygen desaturation index (ODI), and obstructive apnea hypopnea index (OAH)
Statistical analysis	Multiple linear regression without adjustment for collinearity	Multiple negative binomial regression with tests for collinearity