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Brief Communication

# Overnight oxygen desaturation index in sickle cell disease: prediction of sleep apnea

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## 1. Introduction

In sickle cell disease (SCD), there is a reported prevalence of sleep apnea [apnea hypopnea index (AHI) $\geq$5] up to 44% in adults [1]. Full in-lab polysomnogram (PSG) is the gold standard for sleep apnea diagnosis; however, it is associated with significant cost and limited availability. National Heart, Lung and Blood Institute (NHLBI) guidelines recommend screening for obstructive sleep apnea (OSA) symptoms in SCD patients [2], but typical symptoms (eg, snoring) and demographic characteristics (eg, obesity) may be absent in SCD patients with OSA [3]. Although overnight pulse oximetry (OPO) is used to detect nocturnal hypoxemia in SCD patients, the utility of this test in providing evidence for sleep apnea is not established. Available literature on this subject in the general population [4–6] may not be applicable to SCD patients. For instance, nocturnal desaturation may be independent of obstructive events in SCD [7]. Moreover, the oxygen hemoglobin dissociation curve of blood from those with sickle cell anemia is significantly shifted to the right compared to normal subjects [8], calling into question whether oxygen desaturation overestimates respiratory events in subjects with sickle cell anemia. Here, we evaluate whether oxygen desaturation index (ODI) and physician waveform interpretation provide evidence of sleep apnea in this unique population.

## 2. Methods

This is a single-center, retrospective cross-sectional review of 46 adult patients (ages greater than 18 years) with SCD who underwent PSG for signs or symptoms of sleep disordered breathing (nighttime pain, snoring, early morning headache, priapism, and/or nocturnal hypoxemia) over a period of two years. These data have resulted in a previous publication about whether nocturnal hypoxemia was correlated with reticulocytosis [9]. Three patients were excluded because PSG raw data could not be accessed. PSG's were scored in accordance with the 2012 AASM (American Academy of Sleep Medicine) guidelines [10]. Oximetry metrics and AHI, from visually confirmed events, were collected from PSG reports. $ODI_{3\%}$ was calculated by dividing the number of 3% oxygen desaturation over the recording time of the sleep study. Oxygen saturation waveforms were extracted from PSG hypnograms and presented to two board certified sleep physicians who were blinded to the results of the PSG's. Physicians were asked to determine whether the waveform was negative, indeterminate or positive for sleep apnea by visual pattern recognition. STATA 12.0 software was used to calculate Pearson correlations and inter-rater reliability kappa statistic, and to generate a Bland–Altman plot and receiver operator curves (ROC). Institutional review board approval was obtained prior to initiation of the study.

## 3. Results

Baseline demographic characteristics were mean age ($\pm$SD): 31.1 $\pm$ 10.2 years, mean BMI ($\pm$SD): 27.2 kg/m$^2$, hemoglobin ID: SS (72.1%), SC (18.6%), SThal (2.3%). Pearson correlations of oximetry parameters and AHI are shown in Table 1. Bland Altman plot (Fig. 1) of the difference (ODI-AHI) and the mean (ODI + AHI)/2 suggested

*Abbreviations:* AHI, Apnea Hypopnea Index; AASM, American Academy of Sleep Medicine; NHLBI, National Heart, Lung and Blood Institute; ODI, oxygen desaturation index; OPO, overnight pulse oximetry; OSA, obstructive sleep apnea; PSG, polysomnogram; ROC, received operator curve; ROCAUC, receiver operator curve area under the curve; SCD, sickle cell disease.

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**Table 1**
Pearson correlation between oximetry parameters and AHI.

| | Pearson Correlation | P value |
|---|---|---|
| 3% ODI | 0.98 | <0.001 |
| Mean Saturation | −0.06 | 0.702 |
| % Sleep time with Saturation <90% | 0.10 | 0.511 |
| Nadir Saturation | −0.25 | 0.113 |

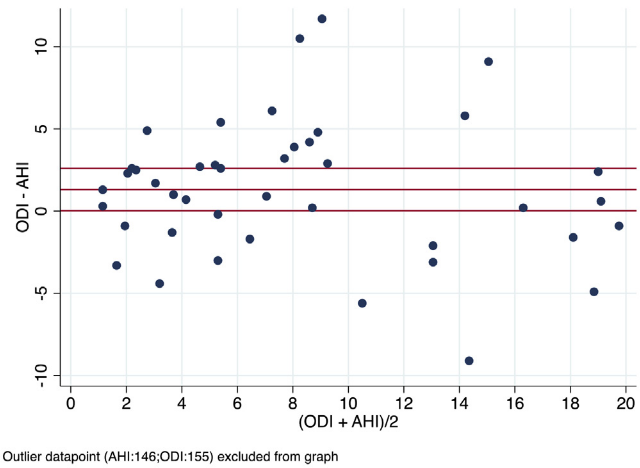


**Fig. 1.** Bland Altman plot of the difference between 3%ODI and AHI versus their mean.

relative agreement between AHI and $ODI_{3\%}$ within five events per hour at lower mean values (less than eight events/hour) and more dispersion of the difference data points away from 0 at higher mean values.

The ROCAUC for $ODI_{3\%}$ was 0.84 (95%CI: 0.72–0.96) and 0.93 (95% CI: 0.85–1.00) for detecting AHI ≥ 5 and AHI≥ 15 respectively. In those with mean saturation >93%, the highest accuracy for predicting AHI ≥5 was with $ODI_{3\%}$ cutoff ≥5 (sensitivity 86.67%, specificity 75.00%, accuracy 81.48%) while the highest accuracy for predicting AHI ≥ 15 was $ODI_{3\%}$ cutoff ≥ 16 (sensitivity 60.00%, specificity 95.45%, accuracy 88.89%). In this group, $ODI_{3\%}$ cutoff of ≥10 was associated with excellent sensitivity of 100.00% and a specificity of 77.27% for predicting AHI ≥15. In those with mean saturation ≤93%, the cutoff of $ODI_{3\%} \geq 9$ was associated with the highest accuracy (sensitivity 100.00%, specificity 71.43%, accuracy 87.50%) for predicting AHI ≥ 5, while the cutoff of $ODI_{3\%} \geq 15$ was associated with the highest accuracy (sensitivity 100.00%, specificity 83.33%, accuracy 87.50%) for predicting AHI ≥ 15. In this group, $ODI_{3\%} \geq 10$ was associated with 100% sensitivity, but specificity was 58.3% for predicting AHI ≥15.

ROC AUC for positive or indeterminate saturation waveform for sleep apnea was 0.62 (95%CI: 0.48–0.76) for the first rater and 0.73 (95%:0.58–0.87) for the second rater for detecting AHI ≥ 5, and 0.61 (95%CI: 0.41–0.80) for the first rater and 0.73 (95% CI: 0.56–0.90) for the second rater for detecting AHI ≥ 15. The inter-rater reliability between the two raters was fair (kappa statistic 0.28; p value = 0.02) for a visual interpretation of a waveform as positive or indeterminate for sleep apnea.

## 4. Discussion

Nocturnal oximetry parameters other than ODI ie mean saturation, cumulative time with oxygen saturation <90%, and nadir saturation have been previously incorporated in AHI prediction model based on oximetry indices in a non-SCD population [5], nevertheless, we found weak to no correlation between these parameters and AHI. About one third (37.2%) of the subjects included in this study had low mean saturation (≤93%) with median AHI 6.1. Time spent below 90% oxygen saturation and low mean oxygen saturation in this group of subjects are markers of increased morbidity [9] but are not predictors of sleep apnea. On the other hand, this study shows that $ODI_{3\%}$ remains a good metric of sleep apnea in this population. Moreover, our findings suggest a relative agreement between AHI and $ODI_{3\%}$ within five events per hour at lower (ODI + AHI)/2 values (less than eight events per hour). This finding is clinically relevant since a relatively low ODI on an OPO can be reassuring. However, it is important to bear in mind that those with decreased sleep time to recording time ratio can have false negative OPO studies for sleep apnea. In addition, the ROC subgroup analysis suggest that an $ODI_{3\%}$ cutoff value of 10 may be applicable for SCD patients with mean saturation >93% for detecting moderate to severe sleep apnea. The cutoff ODI value for those with low mean saturation ≤93% may be higher as noted in this study and as expected based on the oxygen hemoglobin dissociation curve. Finally, the inter-rater reliability for waveform interpretation was fair to poor and its accuracy was modest for the detection of moderate to severe sleep apnea. We still recommend paying close attention to saturation waveforms for clues pointing towards sleep apnea but we do acknowledge that saturation waveform interpretation can have considerable variability among experienced sleep physicians.

A major limitation of this study is that the oximetry data are derived from in-lab PSG's and therefore less likely to have artifact and may have higher resolution compared to home OPO's. High quality overnight pulse oximetry with high resolution is necessary to evaluate oxygen desaturations due to sleep apnea, especially in the setting of baseline hypoxemia commonly seen in patients with sickle cell disease. Moreover, the conclusions of this study are based on a single-center retrospective cross-sectional review of 46 patients and the results need to be replicated in a prospective study.

In conclusion, $ODI_{3\%}$ remains a good predictor of sleep apnea in SCD patients. Although, the main use of OPO in this population is detection of nocturnal hypoxemia which is likely a marker of increased morbidity, physicians can also utilize oximetry for sleep apnea evaluation.

## Author disclosures

Mirna Ayache: no disclosures, no conflict of interest.

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*Role of authors*

1 Mirna Ayache: research question and design, data collection, data analysis, manuscript preparation.
2 Carol Rosen: data collection, interpretation of analysis, manuscript preparation.
3 Ambrose Chiang: data collection, interpretation of analysis, manuscript preparation.
4 Jane Little: hypothesis generation, data collection, manuscript preparation.

5 Kingman Strohl: hypothesis generation, interpretation of analysis, manuscript preparation.

First author Mirna Ayache takes responsibility for the integrity of the research (paper guarantor).

## Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.06.007.

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