# Oxyhemoglobin Saturation Overshoot Following Obstructive Breathing Events Mitigates Sleep Apnea-Induced Glucose Elevations

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**Background:** Obstructive sleep apnea (OSA) and nocturnal hypoxia are associated with disturbances in glucose regulation and diabetes. Temporal associations between OSA, oxygenation profiles and glucose have not been well-described. We hypothesized that oxyhemoglobin desaturation during apneic events and subsequent post-apnea saturation overshoot predict nocturnal glucose.

**Methods:** In 30 OSA patients who underwent polysomnography while subjected to CPAP withdrawal, we characterized $S_PO_2$ swings by frequency, desaturation depth, and overshoot height relative to baseline. We examined the associations between frequently sampled glucose and $S_PO_2$ swings during the preceding 10 min. We developed multi-variable mixed effects linear regression to examine the independent associations between glucose and each level of these $S_PO_2$ swings, while controlling for OSA severity.

**Results:** Desaturation depth was not associated with glucose ($p > 0.05$). In contrast, overshoot was associated with glucose in a dose-dependent manner. Each $S_PO_2$ peak that did not rise to within 1% of baseline was associated with incremental glucose elevations of 0.49 mg/dL ($p = 0.01$), whereas peaks that exceeded baseline by >1% were associated with glucose reductions of 0.46 mg/dL. Overshoot remained an independent predictor of glucose after adjustment for mean $S_PO_2$ and OSA severity ($p > 0.05$).

**Conclusions:** Vigorous $S_PO_2$ improvements after apneic events may protect patients against OSA-related glucose elevations.

Keywords: intermittent, hypoxia, metabolism, automated, phenotype

## INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disease (1–3), which is associated with disturbances in glucose regulation including risks of type 2 diabetes (4–9). Intermittent closure of the upper airway in OSA causes hypoxia, sleep fragmentation and large intrathoracic pressure swings. Hypoxia may be an important stimulus for impaired glucose metabolism. In high altitude residents who are chronically exposed to ambient hypoxia, oxyhemoglobin saturation is associated with increased fasting glucose and glucose intolerance (10, 11). Investigators have also demonstrated that OSA-induced hypoxia was associated with glucose intolerance (7, 12).

Furthermore, exposure to sustained or intermittent hypoxemia causes glucose intolerance and insulin resistance in human and animal experiments (13–16). In a recent study, we sampled blood at 20-min intervals during full polysomnography in CPAP-adherent OSA patients after discontinuing CPAP for 3 nights. During acute exposure to OSA, we observed that dynamic glucose elevations were closely preceded by periods of hypoxia, as assessed by the frequency of desaturations or median oxyhemoglobin saturation ($S_PO_2$) (17). These findings suggest rapid effects of OSA-related hypoxia on plasma glucose levels during sleep. Similarly, in a recent cross-sectional study in high altitude residents who are chronically exposed to hypoxia, we found that mean nocturnal $S_PO_2$ is associated with elevated hemoglobin A1c, independent of sleep apnea severity and daytime $S_PO_2$, indicating that nocturnal hypoxia contributes significantly to worsening overall glucose control (18). Nevertheless, the temporal associations between respiratory disturbances, oxygenation swings, and acute alterations in plasma glucose have not been well-described.

In OSA patients, the evolution of oxygenation over the course of the night is highly variable. During sleep, upper airway obstruction leads to falls in ventilation and subsequent oxyhemoglobin desaturation. At the termination of apneic events, arousals from sleep and improvements upper airway patency can result in transient increases in ventilation and oxygenation. The frequency and height of these $S_PO_2$ peaks can be influenced by several factors including ventilatory responses to gas exchange disturbances during apneic events (19), arousability, sympathetic activation, and co-morbid cardiopulmonary disease. These physiologic factors may not be fully reflected by traditional measures of sleep apnea and hypoxia severity including apnea hypopnea index (AHI) and time spent with $S_PO_2 < 90\%$ (T90). Therefore, dynamic oxygenation characteristics including frequency and depth of desaturation and subsequent correction may provide additional provide additional insight into metabolic risk in OSA patients.

We hypothesized that greater degrees of oxygen desaturation are associated with higher glucose, while greater oxygenation improvements after apneic events may protect against these elevations. To examine this hypothesis, we developed an automated approach to characterize oxygenation profiles in OSA patients by quantifying the frequency and height of periodic $S_PO_2$ nadirs and peaks. We then examined the associations between frequently sampled nocturnal plasma glucose levels and hypoxia, OSA severity, and dynamic $S_PO_2$ swings.

## METHODS

The present study is a *post-hoc* analysis of a recent interventional trial of CPAP withdrawal. The recruitment, sleep study recording and blood sampling methods have been previously described (17). Briefly, CPAP-adherent patients with moderate-to-severe sleep apnea (AHI $\geq$ 20) underwent in-laboratory attended polysonography, with and without CPAP. During these studies, we measured glucose by sampling venous blood every 20 min. Because nocturnal glucose levels varied greatly and were distributed in a bimodal pattern between patients with and without diabetes, we limited our current analysis to non-diabetic patients. This study was approved by the Johns Hopkins Institutional Review Board, and all subjects provided informed written consent.
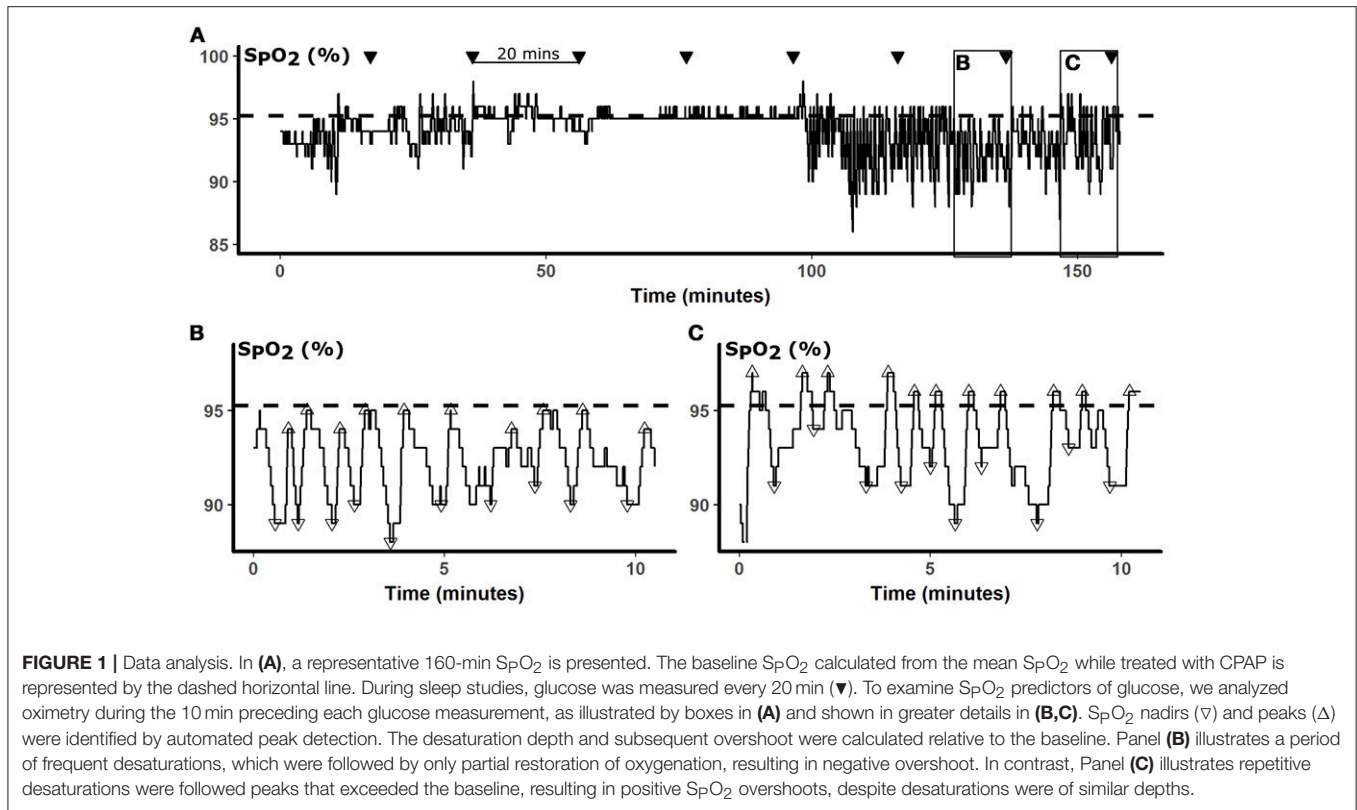
## Data Analysis
### Definitions
Oxyhemogloblin saturation ($S_PO_2$) is dynamic and can vary about a baseline. Thus, we characterized oxygenation profiles by the frequency and amplitude of oxygen oscillations relative to baseline. Because the presence of sleep disordered breathing affects oxyhemoglobin saturation, we defined the baseline saturation as the mean $S_PO_2$ during treatment with CPAP, which resulted in stable respiratory patterns and oxygenation. This method also accounts for differences in lung function or co-morbidities that may also affect $S_PO_2$. **Figure 1** illustrates the relationship between oxygenation in an OSA patient with repetitive apneic episodes, and the CPAP-treated baseline $S_PO_2$, which approximates oxygenation during stable breathing.

To detect acute changes in oxygenation, we applied an automated peak detection algorithm (Matlab, Natick, MA) to identify local $S_PO_2$ minima and maxima during the 10-min windows preceding blood draws (**Figures 1B,C**). Apneic events lead to falls in oxygenation and local oxygenation minima ($\triangledown$). At the termination of apneas and hypopneas, increases in ventilation cause sharp rises in oxygen, resulting in local $S_PO_2$ maxima ($\triangle$), that occasionally exceeded, or overshot, the baseline. Desaturation depths and overshoot heights of these minima and maxima, respectively, were calculated relative to the CPAP baseline. In **Figure 1B**, $S_PO_2$ fell from a baseline $S_PO_2$ of 95% to nadirs of between 89 and 91%, representing desaturation depths of 4–6%. Each of these desaturations was followed by incomplete correction of oxyhemoglobin saturation, to $S_PO_2$ levels of 1–2% below baseline (negative overshoot). In contrast, the frequent desaturations in **Figure 1C** were followed by over-correction of oxygen, exceeding the baseline by 1–3%. We analyzed our data in 10-min windows because sensitivity analyses demonstrated that model performance progressively decayed with increasing windows of 15 and 20 min. Additional sensitivity analyses were performed with progressively increasing lag times between $S_PO_2$ parameters and glucose.

### Analytic Methods
Our primary outcome was nocturnal glucose levels. Our repeated measures design allowed us to examine within- and between-subject changes in glucose, in association with variations in oxygenation and OSA severity. To minimize confounding from periods of wakefulness, we censored glucose measurements that were preceded by >30 s (5%) of wakefulness within 10 min of blood sampling. The 30-s threshold was chosen because blood sampling may occur in the middle of a 30-s scoring epoch, which would reduce the number epochs from 20 to 19. We compared glucose levels during periods with high and low overshoot heights and desaturation depths, using median

**FIGURE 1 |** Data analysis. In **(A)**, a representative 160-min $S_PO_2$ is presented. The baseline $S_PO_2$ calculated from the mean $S_PO_2$ while treated with CPAP is represented by the dashed horizontal line. During sleep studies, glucose was measured every 20 min (▼). To examine $S_PO_2$ predictors of glucose, we analyzed oximetry during the 10 min preceding each glucose measurement, as illustrated by boxes in **(A)** and shown in greater details in **(B,C)**. $S_PO_2$ nadirs (∇) and peaks (Δ) were identified by automated peak detection. The desaturation depth and subsequent overshoot were calculated relative to the baseline. Panel **(B)** illustrates a period of frequent desaturations, which were followed by only partial restoration of oxygenation, resulting in negative overshoot. In contrast, Panel **(C)** illustrates repetitive desaturations were followed peaks that exceeded the baseline, resulting in positive $S_PO_2$ overshoots, despite desaturations were of similar depths.

overshoot (0.3%) and desaturation depth (5%) as the cutoffs. We stratified these analyses by periods with greater or less than the median number of apneic episodes in 10 min (7, which corresponds to an AHI of 42 episodes/h). In these analyses, we modeled glucose as a function of the density of apneic episodes (<7 vs. ≥7), high vs. low mean overshoot or desaturation depth, and their interaction with mixed-effects linear regression models. To further examine the association between nocturnal glucose levels and the frequency and degree of overshoot and desaturation, we developed univariable mixed-effects linear regression models of glucose at each point as functions of the number of overshoots of <−1, ≥−1 and <0, ≥0 and <1, and ≥1% during the preceding 10 min. Similar analyses were performed with desaturations at cutoffs of ≥4 and <5, ≥5 and <6, ≥6 and <7, and ≥7% cutoffs. To account for the effects of hypoxia on nocturnal plasma glucose, we developed multivariable regression models to adjust for mean $S_PO_2$ preceding the glucose measurements. We then performed sensitivity analyses to examine the effect of including glucose measurements in the results. Data analyses were performed in R (www.r-project.org) with the "Linear Mixed-Effects Models using 'Eigen' and S4" package.

## RESULTS

### Subject Baseline Characteristics

Baseline subject characteristics are presented in **Table 1**. Thirty subjects met criteria for inclusion. The majority of subjects were
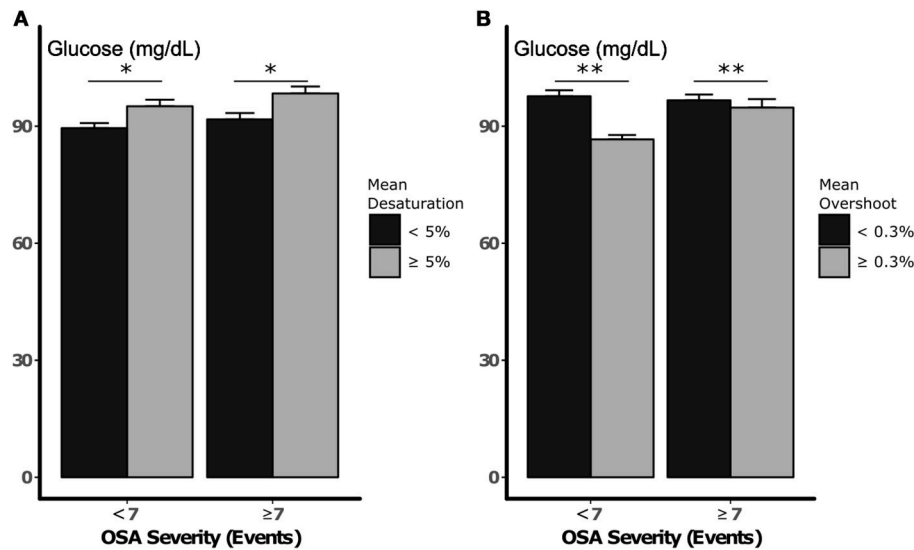
**TABLE 1 |** Demographic and polysomnographic characteristics.

| Characteristic | Mean (SD) |
| --- | --- |
| $N$ | 30 |
| Male sex [$n$ (%)] | 21 (70.0) |
| Observations per subject | 10.77 (4.34) |
| Age (years) | 48.83 (10.43) |
| BMI (kg/m$^2$) | 37.03 (7.88) |
| Sleep apnea severity (AHI) (events/h) | 46.57 (29.18) |
| Time with $S_PO_2$ < 90 (minutes) | 17.09 (19.13) |
| Mean $S_PO_2$ (%) | 93.18 (2.01) |

male. On average, our subjects were middle aged and obese. OSA was present to a severe degree, with time with $S_PO_2$ < 90% for almost 20 min, on average.

## Associations Between Desaturation Depth and Overshoot and Plasma Glucose During Periods of High and Low Apnea Density

**Figure 2A** illustrates glucose after periods of low and high densities of apneic events (greater than or less than 7 events per 10 min, respectively), with low and high mean desaturations. Glucose was higher after periods with greater falls in saturation regardless of event frequency (> 7 vs. <7 apneas or hypopneas per period), although this difference did not exceed the threshold for statistical significance ($p = 0.09$). Neither independent

FIGURE 2 | Nocturnal glucose vs. desaturation depth (A) and $S_PO_2$ overshoot (B), during periods of low and high sleep apnea density. Error bars represent standard errors. *$p < 0.10$ and **$p < 0.05$, respectively, for independent association between mean desaturation depth and $S_PO_2$ and nocturnal glucose. Statistical analysis did not demonstrate an independent or interactive association between sleep apnea density and glucose during sleep.

association between sleep apnea density and glucose nor an interaction between desaturation and sleep apnea density was detected ($p = 0.48$ and 0.52, respectively). On the other hand, greater compared to less overshoot was independently associated with a 4.9 mg/dL reduction in glucose ($p = 0.01$, **Figure 2B**). In these analyses, an independent association between sleep apnea density and glucose was not observed, nor was there an interaction between sleep apnea density and $S_PO_2$ overshoot ($p = 0.88$ and 0.34, respectively). Sensitivity analysis with inclusion of periods of decreased sleep efficiency did not significantly alter these results.

### Independent Associations Between Nocturnal Glucose and Desaturation and Oxygenation Overshoot Frequency at Varying Levels of Intensity

The association between desaturation frequency at varying levels and nocturnal glucose is illustrated in **Figure 3A**. We did not observe a significant association between the depth of desaturation and glucose. Nevertheless, all beta coefficients were similar and approached the threshold for significance ($p = 0.07$) when all desaturation levels were pooled prior to analysis (see $supplement). In contrast, overshoot height predicted glucose in a dose-dependent manner (**Figure 3B**). At negative levels of $S_PO_2$ overshoot (i.e., when $S_PO_2$ did not return to within 1% of the baseline after an apneic episode), each $S_PO_2$ peak during the preceding 10 min was associated with an incremental increase in glucose of 0.49 mg/dL. With greater degrees of overshoot, the incremental change in glucose associated with each apneic event progressively fell. In fact, vigorous overshoots that exceeded baseline saturation by $\geq$1% were associated with reductions in

glucose of 0.46 mg/dL ($p = 0.03$). In multi-variable models that incorporated all levels of $S_PO_2$ overshoot, very low levels of overshoot ($<$−1%) were independently associated with increases in glucose (**Table 2**). In these models, we observed a trend between $\geq$1% overshoot above the baseline and reductions in glucose ($p = 0.07$). The associations between $\geq$1% overshoot and lower glucose was significant after adjustment for traditional metrics of sleep-disordered breathing, including sleep disordered breathing frequency and mean $S_PO_2$. The associations between partial oxygenation correction ($<$−1% overshoot) with increased glucose was not significant with these adjustments because of collinearity with mean $S_PO_2$. These findings suggest that the degree of oxygenation overshoot, but not desaturation depth, after apneic events is a robust predictor of nocturnal glucose.

## DISCUSSION

In the present study, we examined OSA-related hypoxia profiles and their association with glucose during sleep. The novel finding of the study is that the pattern of hypoxia is an important predictor of the overall effect of hypoxia on nocturnal glucose level. Greater $S_PO_2$ overshoot was dose-dependently associated with lower glucose, independent of mean $S_PO_2$ or the frequency of sleep apnea events. As expected, acute hypoxia was also dynamically associated with elevated plasma glucose. Interestingly, there was no relationship between the frequency of OSA events or desaturation depth after these events, and nocturnal plasma glucose levels. Taken together, OSA characterized by nocturnal hypoxia and infrequent and incomplete restoration of oxygenation reflects a phenotype that may be more vulnerable to nocturnal glucose elevation.
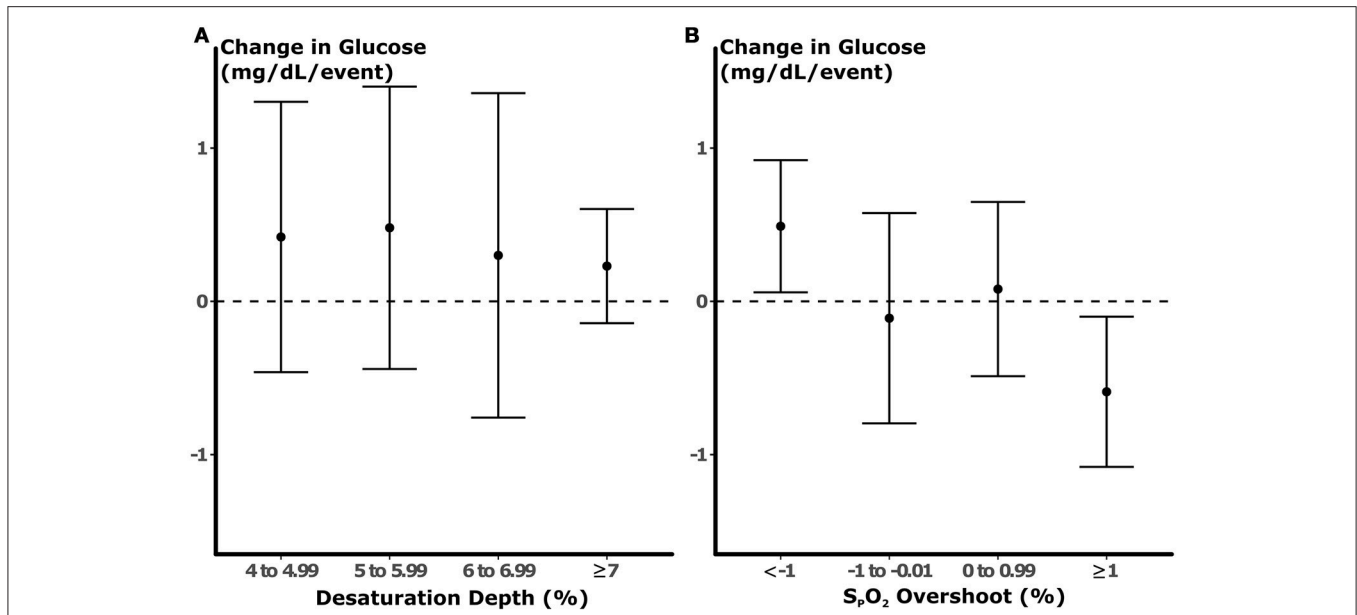
**FIGURE 3 |** Results of univariable models of glucose. Each point represents the change in glucose (±95% confidence interval) predicted by the number of desaturation **(A)** or overshoot **(B)** during the preceding 10 min prior to blood sampling. No statistically significant association was observed between desaturation depth and glucose. In contrast, each apneic episode that was followed by partial normalization of oxygenation was associated with an increase in glucose by 0.49 mg/dL. With increasing degrees of $S_PO_2$ overshoot, the changes in glucose related to each event fell, and $S_PO_2$ peaks that exceeded baseline by >1% were associated with reductions in glucose.

**TABLE 2 |** Regression models of associations between plasma glucose and $S_PO_2$ overshoot and sleep disordered breathing severity.

| Predictor | Uni-variable models | | Multi-variable model 1 | | Multi-variable model 2 | |
|---|---|---|---|---|---|---|
| | Beta | p-value | Beta | p-value | Beta | p-value |
| $S_PO_2$ Overshoot | | | | | | |
| <−1% | 0.49 | 0.01 | 0.42 | 0.04 | 0.24 | 0.33 |
| −1 to (−0.01)% | −0.11 | 0.77 | −0.01 | 0.67 | – | – |
| 0 – 0.99% | −0.14 | 0.54 | −0.00 | 0.99 | – | – |
| ≥1% | −0.46 | 0.03 | −0.40 | 0.07 | −0.46 | < 0.05 |
| Mean $S_PO_2$ | −0.89 | 0.005 | – | – | −0.63 | 0.08 |
| Apneas and hypopneas | 0.10 | 0.36 | – | – | 0.10 | 0.40 |

Conversely, large $S_PO_2$ overshoot may blunt the impact of sleep disordered breathing on nocturnal glucose in OSA patients.

Several mechanisms may explain the links between oxygenation profiles and OSA-related glucose disturbances. First, episodic oxygen restoration may mitigate nocturnal hypoxia related to apneic events. Frequent intermittent oxygen rises may be indicative of frequent arousals, which shorten apnea and hypopnea duration (20–22). In addition, large inspiratory efforts preceding brisk $S_PO_2$ rises could also increase oxygen stores in the lungs and diminish subsequent desaturations. Second, vigorous overshoot could be a marker of arousal and/or lighter sleep, which limits the likelihood of developing additional apneic events and metabolic disturbances (23). In fact, the association between $S_PO_2$ overshoot of >1% and

glucose lowering did not attenuate with adjustment for mean nocturnal $S_PO_2$, suggesting that $S_PO_2$ overshoot may reduce plasma glucose through mechanisms independent of hypoxia. Alternatively, the degree of hypoxia during apneic events and subsequent overshoot could be influenced by comorbidities (24–28). For example, patients with visceral obesity or cardio-pulmonary dysfunction may exhibit both blunted $S_PO_2$ rises and higher glucose excursions after apneic episodes.

In contrast to $S_PO_2$ overshoot, desaturation depth was not related to the degree of glucose change. Further analyses with commonly clinically reported metrics of hypoxia severity including time with $S_PO_2 < 90\%$ also did not predict nocturnal glucose (data not shown). The present study also did not demonstrate an association between OSA events and dynamic nocturnal glucose changes. These findings imply that existing

metrics of OSA severity and related hypoxia do not adequately predict the glycemic impact of sleep disordered breathing. In contrast to previous approaches to characterizing nocturnal hypoxia, we implemented a readily deployable, automated algorithm that focuses on a novel dimension of the oxygenation profile that captures the additional physiologic responses to sleep disordered breathing. Our study demonstrates that frequency and degree of oxygenation overshoots is an important predictor of OSA-related metabolic sequelae, independent of traditional measures of sleep apnea severity.

Our study has several limitations, which are worth considering when interpreting the results. First, the observational nature of our study limits causal inferences. Nevertheless, we demonstrated that alterations in mean $S_PO_2$ and $S_PO_2$ overshoot occurred before changes in nocturnal glucose. Moreover, $S_PO_2$ overshoot predicted nocturnal glucose changes in a dose-dependent manner. These findings are consistent with the notion that hypoxia causes glucose elevations, which can be mitigated by intermittent improvements in oxygenation. Second, our method defines baseline $S_PO_2$ from polysonography while treated with CPAP. The requirement for stable respiratory patterns on a separate night may limit the ability to deploy our methods to estimate metabolic risk in a clinical setting. CPAP may also increase lung volumes and improve baseline $S_PO_2$ [29]. Nevertheless, low lung volumes and attendant $S_PO_2$ reductions may be part of the causal pathway in the pathogenesis of OSA-related hyperglycemia. Third, we examined the relationship between oxygenation and glucose profiles in non-diabetic patients with moderate-to-severe OSA. Additional studies are required to determine the generalizability of these methods to patients with diabetes and/or mild disease by AHI criteria.

## CONCLUSIONS

In summary, our study demonstrated that intermittent restoration of $S_PO_2$ was independently associated with dynamic nocturnal glucose reductions. In contrast, reductions in mean $S_PO_2$ but not the nadir $S_PO_2$ after apneic events predicted glucose elevations. These findings indicate that nocturnal hypoxia is an important determinant of OSA-related glucose disturbances. Our findings further imply that interventions that improve oxygenation in OSA patients may mitigate nocturnal glucose excursions. Additional studies are required to examine the role of oxygen to prevent worsening glucose control, and prospectively validate the use of oxygenation profile analysis to predict metabolic risk in OSA.

## AUTHOR CONTRIBUTIONS

LP, AS, and JJ contributed to the data analysis and interpretation, and manuscript preparation.

## FUNDING

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