Indices of Hypoxic Stress in Sleep Apnea

To the Editor:

The article by Dr. Polotsky and colleagues (1) is an interesting paper with a wealth of valuable data on sleep apnea in the very obese, but we have concerns over the measure of hypoxic stress. Although many of the significant differences between apneic/nonapneic groups might disappear with an appropriate multiple comparisons correction, the apparent greater relevance of hypoxia to insulin resistance and steatohepatitis, rather than apnea/hypopnea index (AHI) (despite the latter requiring $> 4\%$ SaO_2 dips for part of its definition), certainly deserves further exploration. The index of hypoxic stress used in this article is unusual, the "mean fall in SaO_2 from baseline to nadir during sleep-disordered breathing episodes," an index that takes no account of event frequency (1, or a 100, or more), and is not really a quantitative index of intermittent hypoxia severity. It is, in fact, really a measure of how much oxygen desaturation develops, on average, during all the apneic events. This is a complex interaction of many factors: baseline SaO_2 levels (due to the nonlinear oxygen dissociation curve), oxygen reserves in the lung (dependent on FRC, thus abdominal obesity), metabolic rate during the apnea (rate of removal of oxygen from the lungs), and length of the apneic event (dependent on ventilatory response, arousability, and sleepiness).

Thus the index of intermittent hypoxia used by Polotsky and coworkers is difficult to interpret and influenced by many potential confounders. We are concerned that more conventional measures of recurrent hypoxia, such as the number of $>4\%$ SaO_2 dips, or time below an SaO_2 of 90%, for example, were not reported. It would also be interesting to know whether measures of sleepiness and/or microarousals were independent predictors of insulin resistance and worse liver histology, given the fact that recent articles have found sleepiness to be an important predictor of hypertension and cardiac function in obstructive sleep apnea (OSA). In conclusion, we think it is premature to ascribe increased insulin resistance and worse liver histology to "hypoxic stress" when the index of the latter used is likely to be considerably influenced by several relevant confounders.

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Reference

1. Polotsky VY, Patil SP, Savransky V, Laffan A, Fonti S, Frame LA, Steele KE, Schweitzer MA, Clark JM, Torbenson MS, *et al*. Obstructive sleep apnea, insulin resistance, and steatohepatitis in severe obesity. *Am J Respir Crit Care Med* 2009;179:228–234.

Erratum: Obstructive Sleep Apnea, Insulin Resistance, and Steatohepatitis in Severe Obesity

To the Editor:

We would like to thank Drs. Stradling and Kohler (1) for their thoughtful reading of our article (2). They raised questions about whether additional indices of hypoxic stress predicted insulin resistance. Their questions prompted a thorough reanalysis of our data, which revealed several errors and new insights.

The following errata were discovered in our data. First, obesity was associated with elevations in fasting insulin ($\beta = 0.40 \mu\text{U/ml}$ per 1-kg/m^2 increase in BMI; $P = 0.008$) and homeostasis model assessment (HOMA) index levels ($\beta = 0.09$ HOMA unit per 1-kg/m^2 increase in BMI; $P = 0.022$). (See Figure 1C, herein, which is amended from Figure E1C of our online data supplement.) Second, fasting insulin and HOMA were higher in those with a respiratory disturbance index (RDI) > 15 events/hour compared with those with an RDI < 15 events/hour ($P = 0.056$ and 0.015 , respectively) (see Figure 2 herein, as amended from Figure 1 of our study [2]). RDI was associated with elevations in HOMA ($\beta = 0.022$ HOMA units per increase in RDI of 1 event/hr; $P = 0.044$), but this association was no longer significant after adjustment for BMI and waist circumference. Third, fasting insulin was not elevated in subjects with greater compared with lesser degrees of nocturnal oxyhemoglobin

Figure 1. Regression analysis of associations between C-reactive protein (CRP) and BMI (A), CRP and waist circumference (B), HOMA and BMI (C), HOMA and ΔSaO_2 (D). HOMA was calculated as fasting serum insulin ($\mu\text{U/ml}$) $\times$ fasting blood glucose (mmol/L)/22.5. The nocturnal oxyhemoglobin desaturation, ΔSaO_2 , was characterized by the mean fall in oxyhemoglobin saturation from baseline to nadir during sleep disordered breathing episodes.

Figure 2. Fasting serum glucose, serum insulin, and the homeostasis model assessment index (HOMA) in severely obese individuals with OSA. The HOMA was calculated as fasting serum insulin ($\mu\text{U/ml}$) $\times$ fasting blood glucose (mmol/L)/22.5. (Top) Comparison of patients with the respiratory disturbance index (RDI) of < 15 h and > 15 h ($n = 45$ per group). (Bottom) Comparison of patients with average fall in oxyhemoglobin saturation during apneic events (ΔSaO_2) $< 4.6\%$ and $\geq 4.6\%$ ($n = 45$ per group).

desaturations (ΔSaO_2 , median 4.6%), although HOMA trended upward in the desaturating group ($P = 0.069$). Please note that HOMA and insulin levels were not normally distributed, but that the above relationships remained after appropriately transforming these variables.

As suggested by Drs. Stradling and Kohler, several indices might be utilized to quantify hypoxic stress and predict insulin resistance. As reported in our article (2), ΔSaO_2 predicted HOMA ($\beta = 0.56$ HOMA units per 1% increase in ΔSaO_2 ; $P = 0.002$). (See Figure 1D herein, which is amended from Figure E1D in our online data supplement.) Importantly, ΔSaO_2 predicted HOMA even after adjusting for BMI and waist circumference ($P = 0.01$). In contrast, HOMA was not related to the percentage of sleep time spent with an SaO_2 below 90% (T90%), and only trended upward with the oxygen desaturation index (ODI, based on $\geq 4\%$ dips; $P = 0.06$). Nevertheless, HOMA was related to the standard deviation (SD) of the nocturnal SaO_2 signal, independent of the mean nocturnal SaO_2 , waist, and BMI ($P = 0.05$). The SD may optimally measure the severity of intermittent hypoxia, because unlike the ΔSaO_2 , it incorporates information about both the depth and duration of hypoxemic episodes. Our findings lead us to conclude that insulin resistance was independently associated with obesity, RDI, and the severity of intermittent nocturnal desaturation.

We also found that liver injury and inflammation were related to the severity of nocturnal desaturation, but were not related to sleepiness, as measured by the Epworth Sleepiness Scale score. Thus, intermittent hypoxia as reflected by the SaO_2 SD and fall in SaO_2 was an independent predictor of insulin resistance and liver inflammation in severe obesity.

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