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Sleep-Disordered Breathing and Free Fatty Acid Metabolism

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e-Appendix 1.

SUPPLEMENTARY METHODS

The model of FFA kinetics has previously been described in detail previously (11) and formulated by the following equations:

$$\frac{dR}{dt} = k_c\{G^*(t) - R(t)\}, G(0) = G_b; R(t) = R_0 \quad (1)$$

$$\frac{dFFA}{dt} = S_{FFA}FFA_b\{1 - h(t)\} - k_{FFA}FFA(t), FFA(0) = FFA_b \quad (2)$$

$$G^*(t) = \begin{cases} G(t) - g_s & G(t) < g_s \\ 0 & G(t) \geq g_s \end{cases} \quad (3)$$

$$h(t) = \frac{1}{\left(1 + \frac{\Phi}{R(t)}\right)} \quad (4)$$

where t represents time in minutes after the intravenous bolus of glucose. $G(t)$ with units (mmol/l) is a function obtained by linear interpolation of plasma glucose levels over time. G_b is initial basal glucose prior to the IV bolus with units (mmol/l). Parameter g_s (mmol/l) defines a threshold in plasma glucose concentration. Above this threshold level, plasma glucose enters the remote or inaccessible glucose compartment, $R(t)$ with units (mmol/l). In this model $R(t)$, is the principle controller of FFA lipolysis suppression (Figure 1). The rate constant k_c(1/min), quantifies the appearance of glucose in the remote compartment, $R(t)$, and it also represents its clearance. $FFA(t)$ is the plasma concentration of FFA at time t with units (□mol/l). FFA_b (□mol/l) is the basal FFA plasma levels prior to the initiation of the experiment by a bolus of glucose. $h(t)$ is a unitless function that scales the effect of remote glucose on lipolysis to values between 0 and 1. Parameter Φ is an adjustable Michaelis-Menten type affinitity constant. S_{FFA} is a rate constant with units (1/min). When multiplied by basal FFA, FFA_b, it represents the basal lipolysis rate. K_{FFA} is a rate constant (1/min) whole body plasma clearance of FFA. The specifics of model construction are provided by Boston et al (11).

SUPPLEMENTARY RESULTS

The independent association between the apnea-hypopnea index (AHI) and metrics of free fatty acid (FFA) metabolism were examined using multivariable linear regression analyses and a robust variance estimator. In these analyses, AHI was included as a categorical variable based on quartile cut-points and also a continuous variable. Results from the categorical analysis of AHI in quartiles are presented in the main body of the results. In addition to those analyses, AHI was also examined as a continuous variable. These analyses showed that for every 5-point increase in AHI, Adipo-IR increased by 144.5 μmol•μU/L•ml ($p<0.044$ for regression coefficient relating AHI to Adipo-IR) after adjusting for factors such as age and percent body fat indicating greater degrees of adipocyte insulin resistance with increasing AHI. The lipolysis suppression slope

was also independently associated AHI. For every 5-point increase in AHI, the lipolysis suppression slope decreased by 2.7 x 10^{-2} μmol/L•min ($p<0.001$ for regression coefficient relating AHI to the lipolysis suppression slope) indicating that within increasing SDB severity, lipolysis suppression due to insulin and glucose is less robust. Finally, the rate of rebound in FFA levels was lower with increasing AHI. For every 5-point increase in AHI, the FFA rebound slope was lower by 4.2 x 10^{-2} μmol/L•min ($p<0.0001$ for regression coefficient relating AHI to the lipolysis rebound slope). To ease contextual interpretation of the results derived from the multivariable models, the results section in the main manuscript includes results from the categorical inclusion of AHI and other predictor variables.

Because the exclusionary criteria for the study were designed to minimize confounding from prevalent medical conditions, no study participants were on any oral hypoglycemic agents (e.g., metformin). With regard to other medications such as statins, a total of eight participants out of 118 were on statins (6.7%). The distribution of statin use as a function of AHI quartile was as follows: Q1 (1 participant); Q2 (1 participant), Q3 (1 participant), and Q4 (5 participant). Given the low prevalence of statin use and the fact that the highest prevalence was in the fourth AHI quartile, the likelihood of bias introduced by use of statin use is likely to be negligible. Finally, although data on smoking and alcohol use were collected, there was substantial missingness that would preclude a rigorous assessment of whether smoking or alcohol intake varied as function of AHI.