



RESPONSE TO COMMENT ON LECOULTRE ET AL.

# Ten Nights of Moderate Hypoxia Improves Insulin Sensitivity in Obese Humans.

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We previously reported that 10 nights of moderate hypoxia (~15% O<sub>2</sub>; 10 h per night) improved glucose homeostasis (glucose disposal rate [GDR] during a hyperinsulinemic-euglycemic clamp) in obese men (1). Goossens (2) now raises some important questions about our study and puts forward an intriguing alternate hypothesis to explain our results that nightly hypoxia treatment improves whole-body insulin sensitivity.

First, Goossens points out that the improvement in GDR may be explained by a reduction in food intake and concomitant weight loss. Indeed, altitude-associated hypoxia has been shown to trigger significant reductions in energy intake (3). Although we did not collect information on food intake, study participants were instructed to follow their usual dietary habits. With only mild overnight hypoxia during the 10-day intervention period, it is unlikely that food intake decreased dramatically like it does at high altitude. Although our participants did lose weight, the weight loss was small ( $-1.2 \pm 0.3$  kg;  $P = 0.003$ ), especially considering that hypoxia can impact water balance. Moreover and importantly, the improvement in GDR was not correlated with the amount of weight lost. Our data therefore indicate that hypoxia causes an insulin-sensitizing effect independent of weight loss.

Second, Goossens points out that the improvement in GDR may be due to enhanced insulin-mediated suppression of endogenous glucose production (EGP) rather than to improved skeletal muscle insulin sensitivity. We did measure glucose fluxes before and during the clamp procedure using deuterated glucose infusion. However, due to technical challenges, we successfully completed kinetic studies in only six of the eight subjects, and we did not include this partial data in our original article due to these concerns and concerns about type II error bias. Our partial data tentatively suggest that fasting EGP remained constant after 10 nights of mild hypoxic exposure ( $1.50 \pm 0.27$  vs.  $1.47 \pm 0.22$  mg/kg/min before hypoxia;  $P = 0.69$ ), but EGP was greater suppressed during the clamp ( $83 \pm 14$  vs.  $70 \pm 15\%$ ;  $P = 0.005$ ). As the hypoxia-induced decrease in EGP for the six participants was only  $0.19 \pm 0.13$  mg/kg/min, total-body glucose uptake (GDR + EGP) would still be significantly higher after extrapolating the 83% EGP suppression to the two other participants. Our results therefore suggest an improvement in both extrahepatic and hepatic insulin sensitivity after 10 nights of mild hypoxic exposure.

Finally, Goossens (2) offers an intriguing hypothesis that the decrease in adipose tissue oxygen tension (AT pO<sub>2</sub>) may be associated with the improvements in

whole-body GDR, as recently suggested by their own data showing an inverse relationship between abdominal AT pO<sub>2</sub> and whole-body GDR (4). Accordingly, the decreased oxygen tension in our study could trigger an improvement in metabolic function and oxidative metabolism in adipose tissue, thereafter accompanied by a systemic improvement. However, such a hypothesis is in contradiction with rodent models in which adipose tissue hypoxia induces systemic inflammation and insulin resistance (5). Together, our data and data from Goossens identify the need for further studies examining the physiologic and molecular effects of hypoxia in important tissues for metabolic health, such as muscle, liver, and adipose.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

## References

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